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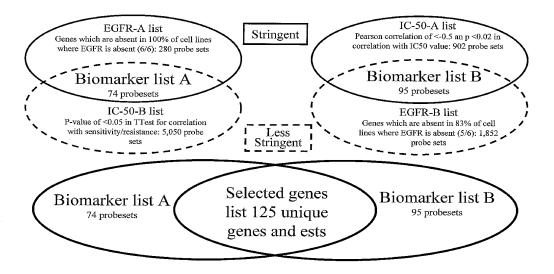
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[Continued on next page]

(54) Title: BIOMARKERS AND METHODS FOR DETERMINING SENSITIVITY TO EPIDERMAL GROWTH FACTOR RECEPTOR MODULATORS



(57) Abstract: EGFR biomakers useful in a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises (a) exposing the mammal to the EGFR modulator and (b) measuring in the mammal level of at least one biomaker, wherein a difference in the level in at least one biomaker measured in (b) compared to the level of the biomaker in a mammal that has not been exposed to the EGFR modulator indicates that the mammal will respond therapeutically to the method of treating cancer.



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BIOMARKERS AND METHODS FOR DETERMINING SENSITIVITY TO EPIDERMAL GROWTH FACTOR RECEPTOR MODULATORS

FIELD OF THE INVENTION

The present invention relates generally to the field of pharmacogenomics, and more specifically to methods and procedures to determine sensitivity in patients to allow the development of individualized genetic profiles which aid in treating diseases and disorders based on patient response at a molecular level.

BACKGROUND OF THE INVENTION:

Cancer is a disease with extensive histoclinical heterogeneity. Although conventional histological and clinical features have been correlated to prognosis, the same apparent prognostic type of tumors varies widely in its responsiveness to therapy and consequent survival of the patient.

New prognostic and predictive markers, which would facilitate an individualization of therapy for each patient, are needed to accurately predict patient response to treatments, such as small molecule or biological molecule drugs, in the clinic. The problem may be solved by the identification of new parameters that could better predict the patient's sensitivity to treatment. The classification of patient samples is a crucial aspect of cancer diagnosis and treatment. The association of a patient's response to a treatment with molecular and genetic markers can open up new opportunities for treatment development in non-responding patients, or distinguish a treatment's indication among other treatment choices because of higher confidence in the efficacy. Further, the pre-selection of patients who are likely to respond well to a medicine, drug, or combination therapy may reduce the number of patients needed in a clinical study or accelerate the time needed to complete a clinical development program (M. Cockett et al., 2000, *Current Opinion in Biotechnology*, 11:602-609).

The ability to predict drug sensitivity in patients is particularly challenging because drug responses reflect not only properties intrinsic to the target cells, but also a host's metabolic properties. Efforts to use genetic information to predict drug sensitivity have primarily focused on individual genes that have broad effects, such as the multidrug resistance genes, *mdr1* and *mrp1* (P. Sonneveld, 2000, *J. Intern. Med.*, 247:521-534).

The development of microarray technologies for large scale characterization of gene mRNA expression pattern has made it possible to systematically search for molecular markers and to categorize cancers into distinct subgroups not evident by traditional histopathological methods (J. Khan et al., 1998, *Cancer Res.*, 58:5009-5013; A.A. Alizadeh et al., 2000, *Nature*, 403:503-511; M. Bittner et al., 2000, *Nature*, 406:536-540; J. Khan et al., 2001, *Nature Medicine*, 7(6):673-679; and T.R. Golub et al., 1999, *Science*, 286:531-537; U. Alon et al., 1999, *Proc. Natl. Acad. Sci. USA*, 96:6745-6750). Such technologies and molecular tools have made it possible to monitor the expression level of a large number of transcripts within a cell population at any given time (see, e.g., Schena et al., 1995, *Science*, 270:467-470; Lockhart et al., 1996, *Nature Biotechnology*, 14:1675-1680; Blanchard et al., 1996, *Nature Biotechnology*, 14:1649; U.S. Patent No. 5,569,588 to Ashby et al.).

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Recent studies demonstrate that gene expression information generated by microarray analysis of human tumors can predict clinical outcome (L.J. van't Veer et al., 2002, *Nature*, 415:530-536; M. West et al., 2001, *Proc. Natl. Acad. Sci. USA*, 98:11462-11467; T. Sorlie et al., 2001, *Proc. Natl. Acad. Sci. USA*, 98:10869-10874; M. Shipp et al., 2002, *Nature Medicine*, 8(1):68-74). These findings bring hope that cancer treatment will be vastly improved by better predicting the response of individual tumors to therapy.

Needed are new and alternative methods and procedures to determine drug sensitivity in patients to allow the development of individualized genetic profiles which are necessary to treat diseases and disorders based on patient response at a molecular level.

SUMMARY OF THE INVENTION:

The invention provides methods and procedures for determining patient sensitivity to one or more Epidermal Growth Factor Receptor (EGFR) modulators. The invention also provides methods of determining or predicting whether an individual requiring therapy for a disease state such as cancer will or will not respond to treatment, prior to administration of the treatment, wherein the treatment comprises one or more EGFR modulators. The one or more EGFR modulators are compounds that can be selected from, for example, one or more EGFR specific ligands, one or

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more small molecule EGFR inhibitors, or one or more EGFR binding monoclonal antibodies.

In one aspect, the invention provides a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises: (a) measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 4; (b) exposing the mammal to the EGFR modulator; (c) following the exposing of step (b), measuring in the mammal the level of the at least one biomarker, wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer.

As used herein, respond therapeutically refers to the alleviation or abrogation of the cancer. This means that the life expectancy of an individual affected with the cancer will be increased or that one or more of the symptoms of the cancer will be reduced or ameliorated. The term encompasses a reduction in cancerous cell growth or tumor volume. Whether a mammal responds therapeutically can be measured by many methods well known in the art, such as PET imaging.

The at least one biomarker can also be selected from the biomarkers of Table 5. The mammal can be, for example, a human, rat, mouse, dog rabbit, pig sheep, cow, horse, cat, primate, or monkey.

The method of the invention can be, for example, an in vitro method and wherein the at least one biomarker is measured in at least one mammalian biological sample from the mammal. The biological sample can comprise, for example, at least one of whole fresh blood, peripheral blood mononuclear cells, frozen whole blood, fresh plasma, frozen plasma, urine, saliva, skin, hair follicle, or tumor tissue.

In another aspect, the invention provides a method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises: (a) exposing the mammal to the EGFR modulator; (b) following the exposing of step (a), measuring in the mammal the level of the at least one biomarker selected from the biomarkers of Table 4, wherein a difference in the level of the at least one biomarker measured in step (b), compared to the level of the biomarker in a mammal that has not been

exposed to said EGFR modulator, indicates that the mammal will respond therapeutically to said method of treating cancer.

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In yet another aspect, the invention provides a method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises: (a) measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 4; (b) exposing the mammal to the EGFR modulator; (c) following the exposing of step (b), measuring in the mammal the level of the at least one biomarker, wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer.

In another aspect, the invention provides a method for determining whether a compound inhibits EGFR activity in a mammal, comprising: (a) exposing the mammal to the compound; and (b) following the exposing of step (a), measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 4, wherein a difference in the level of said biomarker measured in step (b), compared to the level of the biomarker in a mammal that has not been exposed to said compound, indicates that the compound inhibits EGFR activity in the mammal.

In yet another aspect, the invention provides a method for determining whether a mammal has been exposed to a compound that inhibits EGFR activity, comprising (a) exposing the mammal to the compound; and (b) following the exposing of step (a), measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 4, wherein a difference in the level of said biomarker measured in step (b), compared to the level of the biomarker in a mammal that has not been exposed to said compound, indicates that the mammal has been exposed to a compound that inhibits EGFR activity.

In another aspect, the invention provides a method for determining whether a mammal is responding to a compound that inhibits EGFR activity, comprising (a) exposing the mammal to the compound; and (b) following the exposing of step (a), measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 4, wherein a difference in the level of said biomarker measured

in step (b), compared to the level of the biomarker in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits EGFR activity.

As used herein, "responding" encompasses responding by way of a biological and cellular response, as well as a clinical response (such as improved symptoms, a therapeutic effect, or an adverse event), in a mammal

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The invention also provides an isolated biomarker selected from the biomarkers of Table 4. The biomarkers of the invention comprise sequences selected from the nucleotide and amino acid sequences provided in Table 4 and the Sequence Listing, as well as fragments and variants thereof.

The invention also provides a biomarker set comprising two or more biomarkers selected from the biomarkers of Table 4.

The invention also provides kits for determining or predicting whether a patient would be susceptible or resistant to a treatment that comprises one or more EGFR modulators. The patient may have a cancer or tumor such as, for example, a colon cancer or tumor.

In one aspect, the kit comprises a suitable container that comprises one or more specialized microarrays of the invention, one or more EGFR modulators for use in testing cells from patient tissue specimens or patient samples, and instructions for use. The kit may further comprise reagents or materials for monitoring the expression of a biomarker set at the level of mRNA or protein.

In another aspect, the invention provides a kit comprising two or more biomarkers selected from the biomarkers of Table 4.

In yet another aspect, the invention provides a kit comprising at least one of an antibody and a nucleic acid for detecting the presence of at least one of the biomarkers selected from the biomarkers of Table 4. In one aspect, the kit further comprises instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits EGFR activity. In another aspect, the instructions comprise the steps of (a) measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 4, (b) exposing the mammal to the compound, (c) following the exposing of step (b), measuring in the mammal the level of the at least one biomarker,

wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer.

The invention also provides screening assays for determining if a patient will be susceptible or resistant to treatment with one or more EGFR modulators.

The invention also provides a method of monitoring the treatment of a patient having a disease treatable by one or more EGFR modulators.

The invention also provides individualized genetic profiles which are necessary to treat diseases and disorders based on patient response at a molecular level.

The invention also provides specialized microarrays, e.g., oligonucleotide microarrays or cDNA microarrays, comprising one or more biomarkers having expression profiles that correlate with either sensitivity or resistance to one or more EGFR modulators.

The invention also provides antibodies, including polyclonal or monoclonal, directed against one or more biomarkers of the invention.

The invention will be better understood upon a reading of the detailed description of the invention when considered in connection with the accompanying figures.

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BRIEF DESCRIPTION OF THE FIGURES:

FIG. 1 illustrates a EGFR biomarker identification and prioritization strategy. FIG. 2A illustrates the RT-PCR results for EGFR in thirty one colon cancer cell lines to identify cell lines which do not have significant mRNA expression of EGFR.

FIG. 2B illustrates the IC₅₀ profile for twenty two colon cancer cell lines with an EGFR inhibitor compound, and determination of sensitive and resistant cell lines.

DETAILED DESCRIPTION OF THE INVENTION:

The invention provides biomarkers that respond to the modulation of a specific signal transduction pathway and also correlate with EGFR modulator sensitivity or resistance. These biomarkers can be employed for predicting response to one or more EGFR modulators. In one aspect, the biomarkers of the invention are those provided in Table 4 and the Sequence Listing, including both polynucleotide and polypeptide sequences.

The biomarkers were determined by an *in vitro* assay employing microarray technology to monitor simultaneously the expression pattern of thousands of discrete genes in untreated cells, whose response to the modulation of a signal transduction pathway, in particular the EGFR pathway, was tested on untreated cells whose sensitivity to EGFR modulators was tested. The biomarkers have expression levels in the cells that are dependent on the activity of the EFGR signal transduction pathway and that are also highly correlated with EGFR modulator sensitivity exhibited by the cells. Biomarkers serve as useful molecular tools for predicting a response to EGFR modulators, preferably biological molecules, small molecules, and the like that affect EGFR kinase activity via direct or indirect inhibition or antagonism of EGFR kinase function or activity.

20 EGFR MODULATORS

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As used herein, the term "EGFR modulator" is intended to mean a compound or drug that is a biological molecule or a small molecule that directly or indirectly modulates EGFR activity or the EGFR signal transduction pathway. Thus, compounds or drugs as used herein is intended to include both small molecules and biological molecules. Direct or indirect modulation includes activation or inhibition of EGFR activity or the EGFR signal transduction pathway. In one aspect, inhibition refers to inhibition of the binding of EGFR to an EGFR ligand such as, for example, EGF. In another aspect, inhibition refers to inhibition of the kinase activity of EGFR.

EGFR modulators include, for example, EGFR specific ligands, small molecule EGFR inhibitors, and EGFR monoclonal antibodies. In one aspect, the EGFR modulator inhibits EGFR activity and/or inhibits the EGFR signal transduction

pathway. In another aspect, the EGFR modulator is an EGFR antibody that inhibits EGFR activity and/or inhibits the EGFR signal transduction pathway.

EGFR modulators include biological molecules or small molecules. Biological molecules include all lipids and polymers of monosaccharides, amino acids, and nucleotides having a molecular weight greater than 450. Thus, biological molecules include, for example, oligosaccharides and polysaccharides; oligopeptides, polypeptides, peptides, and proteins; and oligonucleotides and polynucleotides. Oligonucleotides and polynucleotides include, for example, DNA and RNA.

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Biological molecules further include derivatives of any of the molecules described above. For example, derivatives of biological molecules include lipid and glycosylation derivatives of oligopeptides, polypeptides, peptides, and proteins.

Derivatives of biological molecules further include lipid derivatives of oligosaccharides and polysaccharides, e.g., lipopolysaccharides. Most typically, biological molecules are antibodies, or functional equivalents of antibodies.

Functional equivalents of antibodies have binding characteristics comparable to those of antibodies, and inhibit the growth of cells that express EGFR. Such functional equivalents include, for example, chimerized, humanized, and single chain antibodies as well as fragments thereof.

Functional equivalents of antibodies also include polypeptides with amino acid sequences substantially the same as the amino acid sequence of the variable or hypervariable regions of the antibodies. An amino acid sequence that is substantially the same as another sequence, but that differs from the other sequence by means of one or more substitutions, additions, and/or deletions, is considered to be an equivalent sequence. Preferably, less than 50%, more preferably less than 25%, and still more preferably less than 10%, of the number of amino acid residues in a sequence are substituted for, added to, or deleted from the protein.

The functional equivalent of an antibody is preferably a chimerized or humanized antibody. A chimerized antibody comprises the variable region of a non-human antibody and the constant region of a human antibody. A humanized antibody comprises the hypervariable region (CDRs) of a non-human antibody. The variable region other than the hypervariable region, e.g., the framework variable region, and the constant region of a humanized antibody are those of a human antibody.

Suitable variable and hypervariable regions of non-human antibodies may be derived from antibodies produced by any non-human mammal in which monoclonal antibodies are made. Suitable examples of mammals other than humans include, for example, rabbits, rats, mice, horses, goats, or primates.

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Functional equivalents further include fragments of antibodies that have binding characteristics that are the same as, or are comparable to, those of the whole antibody. Suitable fragments of the antibody include any fragment that comprises a sufficient portion of the hypervariable (i.e., complementarity determining) region to bind specifically, and with sufficient affinity, to EGFR tyrosine kinase to inhibit growth of cells that express such receptors.

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Such fragments may, for example, contain one or both Fab fragments or the $F(ab')_2$ fragment. Preferably, the antibody fragments contain all six complementarity determining regions of the whole antibody, although functional fragments containing fewer than all of such regions, such as three, four, or five CDRs, are also included.

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In one aspect, the fragments are single chain antibodies, or Fv fragments. Single chain antibodies are polypeptides that comprise at least the variable region of the heavy chain of the antibody linked to the variable region of the light chain, with or without an interconnecting linker. Thus, Fv fragment comprises the entire antibody combining site. These chains may be produced in bacteria or in eukaryotic cells.

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The antibodies and functional equivalents may be members of any class of immunoglobulins, such as IgG, IgM, IgA, IgD, or IgE, and the subclasses thereof. In one aspect, the antibodies are members of the IgG1 subclass. The functional equivalents may also be equivalents of combinations of any of the above classes and subclasses.

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In one aspect, EGFR antibodies can be selected from chimerized, humanized, fully human, and single chain antibodies derived from the murine antibody 225 described in U.S. Patent No. 4,943,533 to Mendelsohn et al. In one aspect, the 225 derived antibodies have the following hypervariable (CDR) regions of the light and heavy chain, wherein the amino acid sequences are indicated below the nucleotide sequences:

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HEAVY CHAIN HYPERVARIABLE REGIONS (VH):

CDR1

AACTATGGTGTACAC (SEQ ID NO: 179)

N Y G V H (SEQ ID NO: 180)

CDR2

5 GTGATATGGAGTGGGAAACACAGACTATAATACACCTTTCACATCC (SEQ ID NO: 181)

VIWSGGNTDYNTPFTS(SEQIDNO: 182)

CDR3

GCCCTCACCTACTATGATTACGAGTTTGCTTAC (SEQ ID NO: 183)

10 ALTYYDYEFAY(SEQ ID NO: 184)

LIGHT CHAIN HYPERVARIABLE REGIONS (VL):

CDR1

AGGGCCAGTCAGAGTATTGGCACAAACATACAC (SEQ ID NO: 185)

15 RASQSIGTNIH (SEQ ID NO: 186)

CDR2

GCTTCTGAGTCTATCTCT (SEQ ID NO: 187)

A S E S I S (SEQ ID NO: 188)

CDR3

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20 CAACAAATAATAACTGGCCAACCACG (SEQ ID NO: 189)

QQNNNWPTT(SEQIDNO: 190)

In another aspect, the EGFR antibody can be selected from the antibodies described in U.S. Patent No. 6,235,883 to Jakobovits et al., U.S. Patent No. 5,558,864 to Bendi et al., and U.S. Patent No. 5,891,996 to Mateo de Acosta del Rio et al.

In addition to the biological molecules discussed above, the EGFR modulators useful in the invention may also be small molecules. Any molecule that is not a biological molecule is considered herein to be a small molecule. Some examples of small molecules include organic compounds, organometallic compounds, salts of organic and organometallic compounds, saccharides, amino acids, and nucleotides. Small molecules further include molecules that would otherwise be considered biological molecules, except their molecular weight is not greater than 450. Thus,

small molecules may be lipids, oligosaccharides, oligopeptides, and oligonucleotides and their derivatives, having a molecular weight of 450 or less.

It is emphasized that small molecules can have any molecular weight. They are merely called small molecules because they typically have molecular weights less than 450. Small molecules include compounds that are found in nature as well as synthetic compounds. In one embodiment, the EGFR modulator is a small molecule that inhibits the growth of tumor cells that express EGFR. In another embodiment, the EGFR modulator is a small molecule that inhibits the growth of refractory tumor cells that express EGFR.

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Numerous small molecules have been described as being useful to inhibit EGFR. For example, U.S. Patent No. 5,656,655 to Spada et al. discloses styryl substituted heteroaryl compounds that inhibit EGFR. The heteroaryl group is a monocyclic ring with one or two heteroatoms, or a bicyclic ring with 1 to about 4 heteroatoms, the compound being optionally substituted or polysubstituted.

U.S. Patent No. 5,646,153 to Spada et al. discloses bis mono and/or bicyclic aryl heteroaryl, carbocyclic, and heterocarbocyclic compounds that inhibit EGFR.

U.S. Patent No. 5,679,683 to Bridges et al. discloses tricyclic pyrimidine compounds that inhibit the EGFR. The compounds are fused heterocyclic pyrimidine derivatives described at column 3, line 35 to column 5, line 6.

U.S. Patent No. 5,616,582 to Barker discloses quinazoline derivatives that have receptor tyrosine kinase inhibitory activity.

Fry et al., Science 265, 1093-1095 (1994) in Figure 1 discloses a compound having a structure that inhibits EGFR.

Osherov et al. disclose tyrphostins that inhibit EGFR/HER1 and HER 2, particularly those in Tables I, II, III, and IV.

U.S. Patent No. 5,196,446 to Levitzki et al. discloses heteroarylethenediyl or heteroarylethendeiylaryl compounds that inhibit EGFR, particularly from column 2, line 42 to column 3, line 40.

Panek et al., Journal of Pharmacology and Experimental Therapeutics 283, 1433-1444 (1997) discloses a compound identified as PD166285 that inhibits the EGFR, PDGFR, and FGFR families of receptors. PD166285 is identified as 6-(2,6-

dichlorophenyl)-2-(4-(2-diethylaminoethyoxy)phenylamino)-8-methyl-8H-pyrido(2,3-d)pyrimidin-7-one having the structure shown in Figure 1 on page 1436.

BIOMARKERS AND BIOMARKER SETS

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The invention includes individual biomarkers and biomarker sets having both diagnostic and prognostic value in disease areas in which signaling through EGFR or the EGFR pathway is of importance, e.g., in cancers or tumors, in immunological disorders, conditions or dysfunction, or in disease states in which cell signaling and/or cellular proliferation controls are abnormal or aberrant. The biomarker sets comprise a plurality of biomarkers such as, for example, a plurality of the biomarkers provided in Table 4 below, that highly correlate with resistance or sensitivity to one or more EGFR modulators.

The biomarker sets of the invention enable one to predict or reasonably foretell the likely effect of one or more EGFR modulators in different biological systems or for cellular responses. The biomarker sets can be used in *in vitro* assays of EGFR modulator response by test cells to predict *in vivo* outcome. In accordance with the invention, the various biomarker sets described herein, or the combination of these biomarker sets with other biomarkers or markers, can be used, for example, to predict how patients with cancer might respond to therapeutic intervention with one or more EGFR modulators.

A biomarker set of cellular gene expression patterns correlating with sensitivity or resistance of cells following exposure of the cells to one or more EGFR modulators provides a useful tool for screening one or tumor samples before treatment with the EGFR modulator. The screening allows a prediction of cells of a tumor sample exposed to one or more EGFR modulators, based on the expression results of the biomarker set, as to whether or not the tumor, and hence a patient harboring the tumor, will or will not respond to treatment with the EGFR modulator.

The biomarker or biomarker set can also be used as described herein for monitoring the progress of disease treatment or therapy in those patients undergoing treatment for a disease involving an EGFR modulator.

The biomarkers serve as targets for the development of therapies for disease treatment. Such targets may be particularly applicable to treatment of breast disease,

such as breast cancers or tumors. Indeed, because these biomarkers are differentially expressed in sensitive and resistant cells, their expression patterns are correlated with relative intrinsic sensitivity of cells to treatment with EGFR modulators.

Accordingly, the biomarkers highly expressed in resistant cells may serve as targets for the development of new therapies for the tumors which are resistant to EGFR modulators, particularly EGFR inhibitors.

MICROARRAYS

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The invention also includes specialized microarrays, e.g., oligonucleotide microarrays or cDNA microarrays, comprising one or more biomarkers, showing expression profiles that correlate with either sensitivity or resistance to one or more EGFR modulators. Such microarrays can be employed in in vitro assays for assessing the expression level of the biomarkers in the test cells from tumor biopsies, and determining whether these test cells are likely to be resistant or sensitive to EGFR modulators. For example, a specialized microarray can be prepared using all the biomarkers, or subsets thereof, as described herein and shown in Table 4. Cells from a tissue or organ biopsy can be isolated and exposed to one or more of the EGFR modulators. Following application of nucleic acids isolated from both untreated and treated cells to one or more of the specialized microarrays, the pattern of gene expression of the tested cells can be determined and compared with that of the biomarker pattern from the control panel of cells used to create the biomarker set on the microarray. Based upon the gene expression pattern results from the cells that underwent testing, it can be determined if the cells show a resistant or a sensitive profile of gene expression. Whether or not the tested cells from a tissue or organ biopsy will respond to one or more of the EGFR modulators and the course of treatment or therapy can then be determined or evaluated based on the information gleaned from the results of the specialized microarray analysis.

ANTIBODIES

The invention also includes antibodies, including polyclonal or monoclonal, directed against one or more of the polypeptide biomarkers. Such antibodies can be used in a variety of ways, for example, to purify, detect, and target the biomarkers of

the invention, including both *in vitro* and *in vivo* diagnostic, detection, screening, and/or therapeutic methods.

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The invention also includes kits for determining or predicting whether a patient would be susceptible or resistant to a treatment that comprises one or more EGFR modulators. The patient may have a cancer or tumor such as, for example, a breast cancer or tumor. Such kits would be useful in a clinical setting for use in testing a patient's biopsied tumor or cancer samples, for example, to determine or predict if the patient's tumor or cancer will be resistant or sensitive to a given treatment or therapy with an EGFR modulator. The kit comprises a suitable container that comprises: one or more microarrays, e.g., oligonucleotide microarrays or cDNA microarrays, that comprise those biomarkers that correlate with resistance and sensitivity to EGFR modulators, particularly EGFR inhibitors; one or more EGFR modulators for use in testing cells from patient tissue specimens or patient samples; and instructions for use. In addition, kits contemplated by the invention can further include, for example, reagents or materials for monitoring the expression of biomarkers of the invention at the level of mRNA or protein, using other techniques and systems practiced in the art such as, for example, RT-PCR assays, which employ primers designed on the basis of one or more of the biomarkers described herein, immunoassays, such as enzyme linked immunosorbent assays (ELISAs), immunoblotting, e.g., Western blots, or in situ hybridization, and the like, as further described herein.

25 APPLICATION OF BIOMARKERS AND BIOMARKER SETS

The biomarkers and biomarker sets may be used in different applications. Biomarker sets can be built from any combination of biomarkers listed in Table 4 to make predictions about the likely effect of any EGFR modulator in different biological systems. The various biomarkers and biomarker sets described herein can be used, for example, as diagnostic or prognostic indicators in disease management, to predict how patients with cancer might respond to therapeutic intervention with compounds that modulate the EGFR, and to predict how patients might respond to

therapeutic intervention that modulates signaling through the entire EGFR regulatory pathway.

While the data described herein were generated in cell lines that are routinely used to screen and identify compounds that have potential utility for cancer therapy, the biomarkers have both diagnostic and prognostic value in other diseases areas in which signaling through EGFR or the EGFR pathway is of importance, e.g., in immunology, or in cancers or tumors in which cell signaling and/or proliferation controls have gone awry.

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In the examples described below, the sensitivity and resistance classifications in the twenty two colon cell lines were similar for the two EGFR modulators tested. Therefore, the biomarkers of the invention are expected to have both diagnostic and prognostic value for other compounds that modulate EGFR or the EGFR signaling pathways.

Those having skill in the pertinent art will appreciate that the EGFR signaling pathway is used and functional in cell types other than cell lines of colon tissue. Therefore, the described biomarkers are expected to have utility for predicting drug sensitivity or resistance to compounds that interact with or inhibit the EGFR activity in cells from other tissues or organs associated with a disease state, or cancers or tumors derived from other tissue types. Non-limiting examples of such cells, tissues and organs include breast, colon, lung, prostate, testes, ovaries, cervix, esophagus, pancreas, spleen, liver, kidney, stomach, lymphocytic and brain, thereby providing a broad and advantageous applicability to the biomarkers described herein. Cells for analysis can be obtained by conventional procedures as known in the art, for example, tissue biopsy, aspiration, sloughed cells, e.g., colonocytes, clinical or medical tissue or cell sampling procedures.

In accordance with the invention, cells from a patient tissue sample, e.g., a tumor or cancer biopsy, can be assayed to determine the expression pattern of one or more biomarkers prior to treatment with one or more EGFR modulators. Success or failure of a treatment can be determined based on the biomarker expression pattern of the cells from the test tissue (test cells), e.g., tumor or cancer biopsy, as being relatively similar or different from the expression pattern of a control set of the one or more biomarkers. Thus, if the test cells show a biomarker expression profile which

corresponds to that of the biomarkers in the control panel of cells which are sensitive to the EGFR modulator, it is highly likely or predicted that the individual's cancer or tumor will respond favorably to treatment with the EGFR modulator. By contrast, if the test cells show a biomarker expression pattern corresponding to that of the biomarkers of the control panel of cells which are resistant to the EGFR modulator, it is highly likely or predicted that the individual's cancer or tumor will not respond to treatment with the EGFR modulator.

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The invention also provides a method of monitoring the treatment of a patient having a disease treatable by one or more EGFR modulators. The isolated test cells from the patient's tissue sample, e.g., a tumor biopsy or tumor sample, can be assayed to determine the expression pattern of one or more biomarkers before and after exposure to an EGFR modulator wherein, preferably, the EGFR modulator is an EGFR inhibitor. The resulting biomarker expression profile of the test cells before and after treatment is compared with that of one or more biomarkers as described and shown herein to be highly expressed in the control panel of cells that are either resistant or sensitive to an EGFR modulator. Thus, if a patient's response is sensitive to treatment by an EGFR modulator, based on correlation of the expression profile of the one or biomarkers, the patient's treatment prognosis can be qualified as favorable and treatment can continue. Also, if, after treatment with an EGFR modulator, the test cells don't show a change in the biomarker expression profile corresponding to the control panel of cells that are sensitive to the EGFR modulator, it can serve as an indicator that the current treatment should be modified, changed, or even discontinued. This monitoring process can indicate success or failure of a patient's treatment with an EGFR modulator and such monitoring processes can be repeated as necessary or desired.

The biomarkers of the invention can be used to predict an outcome prior to having any knowledge about a biological system. Essentially, a biomarker can be considered to be a statistical tool. Biomarkers are useful primarily in predicting the phenotype that is used to classify the biological system. In an embodiment of the invention, the goal of the prediction is to classify cancer cells as having an active or inactive EGFR pathway. Cancer cells with an inactive EGFR pathway can be considered resistant to treatment with an EGFR modulator. An inactive EGFR

pathway is defined herein as a non-significant expression of the EGFR or by a classification as "resistant" or "sensitive" based on the IC₅₀ value of each colon cell line to a compound (EGFR inhibitor compound BMS-461453) exemplified herein.

A number of the biomarker described herein are known to be regulated by EGFR, e.g., mucin 2 (J Biol Chem. 2002 Aug 30;277(35):32258-67). Another biomarker, betacellulin, is know to be an EGFR ligand (Biochem Biophys Res Commun. 2002 Jun 28;294(5):1040-6). A functional relationship of the top biomarkers to the EGFR is expected, since biomarkers that contribute to high biomarker accuracy are likely to play a functional role in the pathway that is being modulated. For example, Perception therapy (i.e., antibody that binds to the Her2 receptor and prevents function via internalization) is indicated when the Her2 gene is overexpressed. It is unlikely that a therapy will have any therapeutic effect if the target enzyme is not expressed.

However, although the complete function of all of the biomarkers are not currently known, some of the biomarkers are likely to be directly or indirectly involved in the EGFR signaling pathway. In addition, some of the biomarkers may function in the metabolic or other resistance pathways specific to the EGFR modulators tested. Notwithstanding, knowledge about the function of the biomarkers is not a requisite for determining the accuracy of a biomarker according to the practice of the invention.

DISCOVERY OF BIOMARKERS

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An approach has been discovered in which biomarkers were identified whose expression patterns, in a subset of cell lines, correlated to and can be used as an *in vitro* marker of cellular response to treatment or therapy with one compound, or with a combination or series of compounds, that are known to inhibit or activate the function of a protein, enzyme, or molecule (e.g., a receptor) that is directly or indirectly involved in cell proliferation, cell responses to external stimuli, (such as ligand binding), or signal transduction, e.g., a receptor tyrosine kinase. Preferred are antagonists or inhibitors of the function of a given protein, e.g., a receptor tyrosine kinase.

Two analytical strategies were deployed to discover biomarkers useful for predicting the sensitivity or resistance of cancer cells to treatment with one or more EGFR modulators. FIG. 1 illustrates the EGFR biomarker identification and prioritization strategy. In one strategy, the mRNA expression level of EGFR was used to identify six colon cancer cell lines with, inferred from the mRNA expression level, no significant presence of the EGFR protein and hence no significant activity of the EGFR pathway (FIG. 2A). In subsequent analyses, biomarkers were identified that had no significant mRNA expression level in the six cell lines and no inferred presence of the EGFR protein. Further, it was required that these biomarkers would have a significant mRNA expression level in at least six other cell lines.

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In a second strategy, an EGFR specific tyrosine kinase inhibitor compound was used to determine compound sensitivity in a panel of twenty two colon cancer cell lines following exposure of the cells to the compound. Some of the cell lines were determined to be resistant to treatment with the inhibitor compound, while others were determined to be sensitive to the inhibitor (FIG. 2B). A subset of the cell lines examined provided an expression pattern or profile of biomarkers that correlated to a response by the cells to the EGFR inhibitor compound as well as the absence of significant EGFR expression as thus could serve as biomarkers.

By combining the use of EGFR co-regulation studies in tumor cells with experimental studies in cultured cells as a model of *in vivo* effects, the invention advantageously focuses on cell-intrinsic properties that are exposed in cell culture to identify biomarkers that predict compound sensitivity and resistance. The discovery and identification of biomarkers in tumor cells and cell lines assayed *in vitro* can be used to predict responses to one or more EGFR modulators *in vivo* and, thus, can be extended to clinical situations in which the same biomarkers are used to predict patients' responses to one or more EGFR modulators and treatments comprising one or more EGFR modulators.

As described in the examples below, oligonucleotide microarrays were used to measure the expression levels of over 44,792 probe sets in a panel of thirty one untreated colon cancer cell lines for which the expression status of the EGFR and the drug sensitivity to EGFR inhibitor compounds was determined. This analysis was performed to determine whether the gene expression signatures of untreated cells

were sufficient for the prediction of sensitivity of the disease to inhibition of the EGFR by small molecule or biological molecule compounds. Through data analysis, biomarkers were identified whose expression levels were found to be highly countercorrelated with the status of the EGFR and correlated with the drug sensitivity. In addition, the treatment of cells with a small molecule EGFR inhibitor also provided gene expression signatures predictive of sensitivity to the compound.

The means of performing the gene expression and biomarker identification analyses embraced by the invention is described in further detail and without limitation below.

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IC₅₀ Determination and Phenotype Classification Based on Sensitivity of Twenty-two Colon Cancer Cell lines to EGFR Inhibitor Compounds

Twenty two colon cell lines were treated with a small molecule EGFR inhibitor (BMS-461453) to determine the individual IC_{50} value. The IC_{50} for each cell line was assessed by MTS assays. The average IC_{50} values along with standard deviations were calculated from two to five individual determinations for each cell line. As shown in FIG. 2B, a 4-fold variation in the IC_{50} values was observed for the small molecule EGFR inhibitor among the 22 colon cancer cell lines. The IC_{50} unit is μM .

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All cell lines with at least a 1.75 fold lower IC_{50} than the most resistant cell lines were considered to be sensitive to treatment with the small molecule EGFR inhibitor. FIG. 2B represents the resistance/sensitivity classifications of the twenty-two colon cell lines to the small molecule EGFR inhibitor. Five cell lines were classified as sensitive and seventeen cell lines as resistant.

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Description of the Strategy for Identifying Biomarkers

Biomarkers were discovered based on two criteria: (i) the correlation of their mRNA expression level to the expression of EGFR in cell lines with insignificant EGFR expression and (ii) the correlation of the IC₅₀ values for the small molecule EGFR inhibitor BMS-461453 with gene expression levels.

For each of these two biomarker selection strategies, two independent "discovery" probe set lists were established by using statistical filters with different

stringency levels to identify genes whose expression correlated with either EGFR status or IC₅₀ value. These statistical methods are described below and resulted in four discovery probe set lists: EGFR-A and EGFR-B (correlation with no significant EGFR expression) and IC-50-A, IC-50-B (correlation with IC₅₀ expression), the Alists containing probe sets selected by more stringent conditions. To then establish two biomarker probe set lists, probe sets that appeared in both EGFR-A and IC-50 B were selected (Biomarker Probe Set List A, Table 2) and probe sets that appeared in both EGFR-B and IC-50-A were selected (Biomarker Probe Set List B, Table 3).

Identifying Genes that Significantly Correlate with EGFR status classification

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RT-PCR expression data for EGFR were obtained from thirty one colon cancer cell lines and six cell lines with a significantly lower expression level of EGFR compared to the other cell lines were identified as described in Example 1 below. (FIG. 2A). Expression profiling data of 44,792 probe sets represented on the HG-U133 array set for all thirty one untreated colon cancer cell lines were obtained and analyzed for the identification of probe sets which would be correlated with the above described six cell lines with no significant mRNA expression of EGFR. For the discovery probe set list EGFR-A, all probe sets which were judged to be absent by the Affymetrix Mas 5.0 software in six of the six colon cancer cell lines with significantly lower expression of EGFR were identified. Second, it was required that these probe sets would be judged to be present in at least six cell lines of the twenty five cell lines classified as having significant mRNA expression of the EGFR. This analytical strategy resulted in the identification of 280 probe sets that could be analyzed in comparison to the discovery probe set list IC-50-B.

The discovery probe set list EGFR-B was generated by selecting all probe sets which were judged to be absent by the Affymetrix Mas 5.0 software in five of the six colon cancer cell lines with significantly lower expression of EGFR and which would be present in at least six cell lines of the twenty five cell lines classified as having significant mRNA expression of the EGFR. Discovery probe set list EGR-B contains 1,852 probe sets (U133A: 876; U133B: 976).

Identifying Genes that Significantly Correlate with Drug Resistance/Sensitivity Classification

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Expression profiling data of 44,792 probe sets represented on the HG-U133 array set for twenty two untreated colon cell lines were obtained and preprocessed as described in Example 1 below. These data were analyzed using the Student's TTEST to identify genes whose expression patterns were strongly correlated with the drug resistance/sensitivity classification. Table 1 provides the resistance/sensitivity phenotype classification of the twenty two colon cell lines for the EGFR antagonist BMS-461453 based on the IC₅₀ results. The mean IC₅₀ values along with standard deviations (SD) were calculated from 2 to 5 individual determinations for each cell line as shown. The mean IC₅₀ across the twenty two colon cell lines for BMS-461453 was calculated and used to normalize the IC₅₀ data for each cell line. All cell lines with at least a 1.75 fold lower IC₅₀ than the most resistant cell lines were considered to be sensitive to treatment with BMS-461453. The cell lines designated with an asterisk are defined as being sensitive to the drug treatment.

TABLE 1 - Resistance/Sensitivity Phenotype Classification of Twenty Two Colon Cell Lines

Cell lines	IC ₅₀ (μM)	SD
CCD_33C0*	2	1.28
LOVO*	2.3	2.28
LS174T*	3.5	1.93
Caco2*	5.5	3.97
SW403*	5.7	4.94
CCD18Co	7.1	3.84
SW837	7.2	3.30
Sk-Co-1	9	2.02
MIP	9.7	0.52
SW1417	10	0.00
HT-29	10	0.00
T84	10	0.00
CX-1	10	0.00
Colo-205	10	0.00
Colo-201	10	0.00
Colo320HSR	10	0.00
HCT8	10	0.00
Colo320DM	10	0.00
SW480	10	0.00
HCT116	10	0.00
SW620	10	0.00
HCT116S542	10	0.00

An "idealized expression pattern" corresponds to a gene that is uniformly high in one class (e.g., sensitive) and uniformly low in the other (e.g., resistant). Initially, a Student TTEST was performed in which a T value was obtained for each probe set.

Once a T value was generated, its corresponding confidence value (P) was found on a standard table of significance. The confidence value is a measure of the probability to observe a certain mean expression difference between two groups by chance alone and is obtained using the following formula:

$$T(g.c) = (X_1 - X_2) / (var_1/n_1 + var_2/n_2)^{1/2}$$

wherein,

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T(g,c) represents the T value between expression for gene g and the sensitivity/resistance classification c;

- 5 X₁ represents mean gene expression level of samples in class 1;
 X₂ represents mean gene expression level of samples in class 2;
 var₁ represents variance of gene expression for samples in class 1;
 var₂ represents variance of gene expression for samples in class 2;
 n₁ represents number of samples in class 1;
- 10 n₂ represents number of samples in class 2; and corresponding confidence value (P) for T values are obtained from a standard table of significance.

To generate discovery probe set list IC-50-B, a confidence value of 0.05 or lower was used as the cut off for probe sets to be included in the list. Discovery probe set list IC-50-B contains 5,050 probe sets (U133A: 2,498; U133B: 2,552).

Discovery probe set list IC-50-A was generated using the Pearson correlation coefficient (a dimensionless index that ranges from -1.0 to 1.0). This value was calculated by treating the IC₅₀ data as continuous variables and by utilizing a linear regression model to correlate gene expression levels with IC₅₀ values for twenty-two colon cell lines. Probe sets with a correlation coefficient less than -0.5 were selected (p <0.02), a total of 902 probe sets (U133A: 467; U133B: 435).

Finally, two separate biomarker probe set lists were generated, biomarker probe set lists A and B, by identifying probe sets which were present in EGFR-A and IC-50-B (Biomarker Probe Set List A) (Table 2) or were present in EGFR-B and IC-50-A (Biomarker Probe Set List B) (Table 3).

The biomarker probe set list A (Table 2) contains a total of 74 probe sets (U133A: 43; U133B: 31) and provides the polynucleotides identified to be biomarkers of EGFR antagonist sensitivity employing strategy A. With strategy A, polynucleotides were required to satisfy a stringent criteria for EGFR status coregulation and a less stringent condition for correlation to IC₅₀ values. Namely, the polynucleotides had to be called absent by the Affymetrix software in six out of the

six cell lines with lowest expression of EGFR and be differentially expressed in the sensitive and resistance cell lines with a P value equal to or less than 0.05.

TABLE 2 - Biomarker Probe Set List A

Unigene Title	Affymetrix Description	Affymetrix
		probe set
hemoglobin,	gb:BC005931.1 /DEF=Homo sapiens,	211745 x at
alpha 1	hemoglobin, alpha 2, clone MGC:14541, mRNA,	
-	complete cds. /FEA=mRNA	
	/PROD=hemoglobin, alpha 2	
	/DB_XREF=gi:13543547 /FL=gb:BC005931.1	
dipeptidylpeptida	gb:M80536.1 /DEF=H.sapiens dipeptidyl	203716 s at
se IV (CD26,	peptidase IV (DPP4) mRNA, complete cds.	
adenosine	/FEA=mRNA /GEN=DPP4 /PROD=dipeptidyl	
deaminase	peptidase IV /DB XREF=gi:181569	
complexing	/UG=Hs.44926 dipeptidylpeptidase IV (CD26,	
protein 2)	adenosine deaminase complexing protein 2)	
	/FL=gb:M80536.1 gb:NM_001935.1	
spondin 1, (f-	Consensus includes gb:AI885290 /FEA=EST	213994 s at
spondin)	/DB_XREF=gi:5590454	
extracellular	/DB XREF=est:wl92a04.x1	
matrix protein	/CLONE=IMAGE:2432334 /UG=Hs.5378	
_	spondin 1, (f-spondin) extracellular matrix	
	protein	
3-hydroxy-3-	gb:NM_005518.1 /DEF=Homo sapiens 3-	204607_at
methylglutaryl-	hydroxy-3-methylglutaryl-Coenzyme A synthase	_
Coenzyme A	2 (mitochondrial) (HMGCS2), mRNA.	
synthase 2	/FEA=mRNA /GEN=HMGCS2 /PROD=3-	
(mitochondrial)	hydroxy-3-methylglutaryl-Coenzyme A synthase	
,	2(mitochondrial) /DB_XREF=gi:5031750	
	/UG=Hs.59889 3-hydroxy-3-methylglutaryl-	
	Coenzyme A synthase 2 (mitochondrial)	
	/FL=gb:NM_005518.1	
mucin 2,	gb:NM_002457.1 /DEF=Homo sapiens mucin 2,	204673 at
intestinal/trachea	intestinaltracheal (MUC2), mRNA. /FEA=mRNA	_
1	/GEN=MUC2 /PROD=mucin 2, intestinaltracheal	
	/DB XREF=gi:4505284 /UG=Hs.315 mucin 2,	
	intestinaltracheal /FL=gb:NM_002457.1	
į į	gb:L21998.1	
cystic fibrosis	gb:NM_000492.2 /DEF=Homo sapiens cystic	205043_at
transmembrane	fibrosis transmembrane conductance regulator,	
conductance	ATP-binding cassette (sub-family C, member 7)	
regulator, ATP-	(CFTR), mRNA. /FEA=mRNA /GEN=CFTR	
binding cassette	/PROD=cystic fibrosis transmembrane	
(sub-family C,	conductanceregulator, ATP-binding cassette (sub-	
member 7)	family C, member 7) /DB_XREF=gi:6995995	

		
'	/UG=Hs.663 cystic fibrosis transmembrane	
	conductance regulator, ATP-binding cassette	
	(sub-family C, member 7) /FL=gb:NM_000492.2	
CUG triplet	Consensus includes gb:N36839 /FEA=EST	202156_s_at
repeat, RNA-	/DB XREF=gi:1157981	
binding protein 2	/DB XREF=est:yy35f07.s1	
J	/CLONE=IMAGE:273253 /UG=Hs.211610 CUG	
	triplet repeat, RNA-binding protein 2	
	/FL=gb:U69546.1 gb:AF036956.1	
	gb:AF090694.1 gb:NM_006561.1	
nuclear receptor	gb:NM 000901.1 /DEF=Homo sapiens nuclear	205259 at
subfamily 3,	receptor subfamily 3, group C, member 2	200200
· ·	(NR3C2), mRNA. /FEA=mRNA /GEN=NR3C2	
group C, member	/PROD=nuclear receptor subfamily 3, group C,	
2		
	member 2 /DB_XREF=gi:4505198 /UG=Hs.1790	
	nuclear receptor subfamily 3, group C, member 2	
	/FL=gb:M16801.1 gb:NM 000901.1	015700
cystic fibrosis	Consensus includes gb:W60595 /FEA=EST	215702_s_at
transmembrane	/DB_XREF=gi:1367354	
conductance	/DB_XREF=est:zc91b04.s1	
regulator, ATP-	/CLONE=IMAGE:338479 /UG=Hs.663 cystic	
binding cassette	fibrosis transmembrane conductance regulator,	
(sub-family C,	ATP-binding cassette (sub-family C, member 7)	
member 7)		
cytochrome	gb:NM_000775.1 /DEF=Homo sapiens	205073_at
P450, subfamily	cytochrome P450, subfamily IIJ (arachidonic acid	
IIJ (arachidonic	epoxygenase) polypeptide 2 (CYP2J2), mRNA.	
acid	/FEA=mRNA /GEN=CYP2J2	
epoxygenase)	/PROD=cytochrome P450, subfamily IIJ	
polypeptide 2	(arachidonic acidepoxygenase) polypeptide 2	
	/DB XREF=gi:4503226 /UG=Hs.152096	
	cytochrome P450, subfamily IIJ (arachidonic acid	
	epoxygenase) polypeptide 2 /FL=gb:U37143.1	
	gb:NM 000775.1	
cystatin S	gb:NM 001899.1 /DEF=Homo sapiens cystatin S	206994 at
Cyblain 5	(CST4), mRNA. /FEA=mRNA /GEN=CST4	_
•	/PROD=cystatin S /DB XREF=gi:4503108	
	/UG=Hs.56319 cystatin S /FL=gb:NM_001899.1	
spondin 1, (f-	Consensus includes gb:AI885290 /FEA=EST	213993 at
· · · · · · · · · · · · · · · · · · ·	/DB XREF=gi:5590454	
spondin) extracellular	/DB_XREF=g1.5590454 /DB_XREF=est:wl92a04.x1	
	/CLONE=IMAGE:2432334 /UG=Hs.5378	1
matrix protein	· · · · · · · · ·	
	spondin 1, (f-spondin) extracellular matrix	
	protein	202628 - 11
fibroblast growth	gb:NM_022969.1 /DEF=Homo sapiens fibroblast	203638_s_at
factor receptor 2	growth factor receptor 2 (bacteria-expressed	
(bacteria-	kinase, keratinocyte growth factor receptor,	
expressed kinase,	craniofacial dysostosis 1, Crouzon syndrome,	

keratinocyte	Pfeiffer syndrome, Jackson-Weiss syndrome)	
growth factor	(FGFR2), transcript variant 2, mRNA.	
•	/FEA=mRNA /GEN=FGFR2 /PROD=fibroblast	
receptor,	growth factor receptor 2, isoform 2precursor	
craniofacial		
dysostosis 1,	/DB_XREF=gi:13186252 /UG=Hs.278581	
Crouzon	fibroblast growth factor receptor 2 (bacteria-	
syndrome,	expressed kinase, keratinocyte growth factor	
Pfeiffer	receptor, craniofacial dysostosis 1, Crouzon	
syndrome,	syndrome, Pfeiffer syndrome, Jackson-Weiss	
Jackson-Weiss	syndrome) /FL=gb:NM_022969.1 gb:M97193.1	
syndrome)	gb:M80634.1	
mucin 3B	Consensus includes gb:AB038783.1 /DEF=Homo	214898_x_at
	sapiens MUC3B mRNA for intestinal mucin,	
	partial cds. /FEA=mRNA /GEN=MUC3B	li.
	/PROD=intestinal mucin /DB XREF=gi:9929917	
	/UG=Hs.129782 mucin 3A, intestinal	
AA	Consensus includes gb:AV728958 /FEA=EST	212703 at
	/DB XREF=gi:10838379	212,05_40
	/DB_XREF=est:AV728958	
i □	/CLONE=HTCBYF04/UG=Hs.150443	
	KIAA0320 protein	2021504
CUG triplet	gb:NM_006561.1 /DEF=Homo sapiens CUG	202158_s_at
repeat, RNA-	triplet repeat, RNA-binding protein 2 (CUGBP2),	
binding protein 2	mRNA. /FEA=mRNA /GEN=CUGBP2	
	/PROD=CUG triplet repeat, RNA-binding protein	
,	2 /DB_XREF=gi:5729815 /UG=Hs.211610 CUG	
	triplet repeat, RNA-binding protein 2	
	/FL=gb:U69546.1 gb:AF036956.1	
	gb:AF090694.1 gb:NM_006561.1	
spondin 1, (f-	gb:AB051390.1 /DEF=Homo sapiens mRNA for	209437_s at
spondin)	VSGPF-spondin, complete cds. /FEA=mRNA	
extracellular	/PROD=VSGPF-spondin	
matrix protein	/DB XREF=gi:11320819 /UG=Hs.5378 spondin	
maan protein	1, (f-spondin) extracellular matrix protein	
	/FL=gb:AB051390.1	
mucin 3B	Consensus includes gb:AF113616 /DEF=Homo	214676 x at
mucm 55	sapiens intestinal mucin 3 (MUC3) gene, partial	21.070_1_40
	cds /FEA=mRNA /DB XREF=gi:6466800	
D 7 4 1	/UG=Hs.129782 mucin 3A, intestinal	205077
EphA1	gb:NM_005232.1 /DEF=Homo sapiens EphA1	205977_s_at
	(EPHA1), mRNA. /FEA=mRNA /GEN=EPHA1	
	/PROD=EphA1 /DB_XREF=gi:4885208	-
	/UG=Hs.89839 EphA1 /FL=gb:M18391.1	
	gb:NM_005232.1	
matrilin 3	gb:NM_002381.2 /DEF=Homo sapiens matrilin 3	206091_at
	(MATN3) precursor, mRNA. /FEA=mRNA	
	/GEN=MATN3 /PROD=matrilin 3 precursor	\
	/DB_XREF=gi:13518040 /UG=Hs.278461	
	<u> </u>	

	matrilin 3 /FL=gb:NM 002381.2	
bone	gb:NM_001200.1 /DEF=Homo sapiens bone	205290 s at
morphogenetic	morphogenetic protein 2 (BMP2), mRNA.	2032)
protein 2	/FEA=mRNA /GEN=BMP2 /PROD=bone	
protein 2	morphogenetic protein 2 precursor	
	/DB XREF=gi:4557368/UG=Hs.73853 bone	
	morphogenetic protein 2 /FL=gb:NM_001200.1	
interferon	Consensus includes gb:AI073984 /FEA=EST	204057 at
	/DB XREF=gi:3400628	204037_ai
consensus		
sequence binding	/DB_XREF=est:0y66c05.x1 /CLONE=IMAGE:1670792 /UG=Hs.14453	
protein 1		'
	interferon consensus sequence binding protein 1	
	/FL=gb:M91196.1 gb:NM_002163.1	221972
retinoic acid	Consensus includes gb:AI669229 /FEA=EST	221872_at
receptor	/DB_XREF=gi:4834003	
responder	/DB_XREF=est:wc13e06.x1	
(tazarotene	/CLONE=IMAGE:2315074 /UG=Hs.82547	
induced) 1	retinoic acid receptor responder (tazarotene	
	induced) 1	21.5502
cystic fibrosis	Consensus includes gb:W60595 /FEA=EST	215703_at
transmembrane	/DB_XREF=gi:1367354	
conductance	/DB_XREF=est:zc91b04.s1	
regulator, ATP-	/CLONE=IMAGE:338479 /UG=Hs.663 cystic	
binding cassette	fibrosis transmembrane conductance regulator,	
(sub-family C,	ATP-binding cassette (sub-family C, member 7)	
member 7)		
fibroblast growth	gb:M87771.1 /DEF=Human secreted fibroblast	208228_s_at
factor receptor 2	growth factor receptor (K-sam-III) mRNA,	
(bacteria-	complete cds. /FEA=mRNA /GEN=K-sam-III	
expressed kinase,	/PROD=fibroblast growth factor receptor	Ì
keratinocyte	/DB_XREF=gi:186781 /UG=Hs.278581	
growth factor	fibroblast growth factor receptor 2 (bacteria-	
receptor,	expressed kinase, keratinocyte growth factor	
craniofacial	receptor, craniofacial dysostosis 1, Crouzon	
dysostosis 1,	syndrome, Pfeiffer syndrome, Jackson-Weiss	
Crouzon	syndrome) /FL=gb:NM_022970.1 gb:M87771.1	
syndrome,		}
Pfeiffer		
syndrome,		
Jackson-Weiss		
syndrome)		
myosin, heavy	gb:NM_003802.1 /DEF=Homo sapiens myosin,	208208_at
polypeptide 13,	heavy polypeptide 13, skeletal muscle (MYH13),	}
skeletal muscle	mRNA. /FEA=mRNA /GEN=MYH13	
	/PROD=myosin, heavy polypeptide 13, skeletal	
	muscle /DB XREF=gi:11321578	1
	/UG=Hs.278488 myosin, heavy polypeptide 13,	1
	skeletal muscle /FL=gb:NM_003802.1	

	gb:AF111782.2	
FOT- W-11-		222254 et
ESTs, Weakly	Consensus includes gb:AW675655 /FEA=EST	222354_at
similar to I38022	/DB_XREF=gi:7540890	
hypothetical	/DB_XREF=est:ba52e01.x1	
protein	/CLONE=IMAGE:2900184 /UG=Hs.314158	
[H.sapiens]	ESTs	
hypothetical	gb:NM_017699.1 /DEF=Homo sapiens	219734_at
protein	hypothetical protein FLJ20174 (FLJ20174),	
FLJ20174	mRNA. /FEA=mRNA /GEN=FLJ20174	
	/PROD=hypothetical protein FLJ20174	
	/DB XREF=gi:8923170 /UG=Hs.114556	
l	hypothetical protein FLJ20174	
	/FL=gb:NM_017699.1	
PTPRF	Consensus includes gb:AI692180 /FEA=EST	212841 s at
interacting	/DB XREF=gi:4969520	212011_5_at
	/DB_AREF=g1.4909320 /DB_XREF=est:wd37f06.x1	
protein, binding	/CLONE=IMAGE:2330339 /UG=Hs.12953	
protein 2 (liprin		
beta 2)	PTPRF interacting protein, binding protein 2	
	(liprin beta 2)	201707
ribonuclease,	gb:NM_002933.1 /DEF=Homo sapiens	201785_at
RNase A family,	ribonuclease, RNase A family, 1 (pancreatic)	
1 (pancreatic)	(RNASE1), mRNA. /FEA=mRNA	
	/GEN=RNASE1 /PROD=ribonuclease, RNase A	
	family, 1 (pancreatic) /DB_XREF=gi:4506546	
	/UG=Hs.78224 ribonuclease, RNase A family, 1	
	(pancreatic) /FL=gb:BC005324.1	
	gb:NM_002933.1 gb:D26129.1	
hairless (mouse)	gb:NM 018411.1 /DEF=Homo sapiens hairless	220163 s at
homolog	protein (putative single zinc finger transcription	
l monnorog	factor protein, responsible for autosomal	
	recessive universal congenital alopecia, HR gene)	ļ
	(HSA277165), mRNA. /FEA=mRNA	
	/GEN=HSA277165 /PROD=hairless protein	1
	/DB_XREF=gi:11036651 /UG=Hs.272367	
	hairless protein (putative single zinc finger	
	transcription factor protein, responsible for	
	autosomal recessive universal congenital	
	alopecia, HR gene) /FL=gb:NM_018411.1	210174 -4
nuclear receptor	Consensus includes gb:AF228413.1 /DEF=Homo	210174_at
subfamily 5,	sapiens hepatocyte transcription factor mRNA,	
group A,	3UTR. /FEA=mRNA /DB_XREF=gi:7677372	
member 2	/UG=Hs.183123 nuclear receptor subfamily 5,	
	group A, member 2 /FL=gb:U93553.1	
	gb:AB019246.1 gb:AF124247.1	
superoxide	gb:NM_003102.1 /DEF=Homo sapiens	205236_x_at
dismutase 3,	superoxide dismutase 3, extracellular (SOD3),	_
extracellular	mRNA. /FEA=mRNA /GEN=SOD3	
	/PROD=superoxide dismutase 3, extracellular	
L		

	/DB_XREF=gi:4507150 /UG=Hs.2420	
	superoxide dismutase 3, extracellular	
	/FL=gb:J02947.1 gb:NM_003102.1	
zinc finger	gb:NM 003438.1 /DEF=Homo sapiens zinc	207394 at
protein 137	finger protein 137 (clone pHZ-30) (ZNF137),	-
(clone pHZ-30)	mRNA. /FEA=mRNA /GEN=ZNF137	
(Clone priz-30)	/PROD=zinc finger protein 137 (clone pHZ-30)	
	/DB XREF=gi:4507988 /UG=Hs.151689 zinc	
	finger protein 137 (clone pHZ-30)	
	/FL=gb:NM_003438.1 gb:U09414.1	217200 -4
Homo sapiens	Consensus includes gb:AL049983.1 /DEF=Homo	217288_at
mRNA; cDNA	sapiens mRNA; cDNA DKFZp564D042 (from	
DKFZp564D042	clone DKFZp564D042). /FEA=mRNA	
(from clone	/DB_XREF=gi:4884234 /UG=Hs.240136 Homo	
DKFZp564D042	sapiens mRNA; cDNA DKFZp564D042 (from	
) -	clone DKFZp564D042)	
Hermansky-	Consensus includes gb:AL022313 /DEF=Human	217354 s at
Pudlak syndrome	DNA sequence from clone RP5-1119A7 on	
1 datak byllarollic	chromosome 22q12.2-12.3 Contains the TXN2	
	gene for mitochondrial thioredoxin, a novel gene,	
	the EIF3S7 gene for eukaryotic translation	
	initiation factor 3 subunit 7 (zeta, 6667kD) (EIF3-	
	P66), the gene f /FEA=CDS_3	
	/DB_XREF=gi:4200326 /UG=Hs.272270 Human	
	DNA sequence from clone RP5-1119A7 on	
	chromosome 22q12.2-12.3 Contains the TXN2	
	gene for mitochondrial thioredoxin, a novel gene,	
	the EIF3S7 gene for eukaryotic translation	
	initiation factor 3 subunit 7 (zeta, 6667kD) (EIF3-	
	P66), the gene for a nov	
peroxisomal	gb:NM 018441.1 /DEF=Homo sapiens	221142_s_at
trans 2-enoyl	peroxisomal trans 2-enoyl CoA reductase;	
CoA reductase;	putative short chain alcohol dehydrogenase	1
putative short	(HSA250303), mRNA. /FEA=mRNA	
chain alcohol	/GEN=HSA250303 /PROD=peroxisomal trans 2-	
dehydrogenase	enoyl CoA reductase; putative short chain alcohol	
denydrogenasc	dehydrogenase /DB_XREF=gi:8923751	ļ
	/UG=Hs.281680 peroxisomal trans 2-enoyl CoA	
	reductase; putative short chain alcohol	
	dehydrogenase /FL=gb:NM_018441.1	201226 a et
BTG family,	gb:NM_006763.1 /DEF=Homo sapiens BTG	201236_s_at
member 2	family, member 2 (BTG2), mRNA. /FEA=mRNA	
	/GEN=BTG2 /PROD=BTG family, member 2	
	/DB_XREF=gi:5802987 /UG=Hs.75462 BTG	
	family, member 2 /FL=gb:U72649.1	
	gb:NM_006763.1	
phosducin	gb:M33478.1 /DEF=Human 33-kDa	211496_s_at
1	phototransducing protein mRNA, complete cds.	

	/FEA=mRNA /DB_XREF=gi:177186	
	/UG=Hs.550 phosducin /FL=gb:NM_022577.1	
	gb:M33478.1 gb:AF076465.1	20,7000
Rho GTPase	gb:NM_015366.1 /DEF=Homo sapiens Rho	205980_s_at
activating protein	GTPase activating protein 8 (ARHGAP8),	
8	mRNA. /FEA=mRNA /GEN=ARHGAP8	
	/PROD=Rho GTPase activating protein 8	
	/DB_XREF=gi:7656903 /UG=Hs.102336 Rho	
	GTPase activating protein 8	
	/FL=gb:NM_015366.1	010056
Homo sapiens	Consensus includes gb:AW593996 /FEA=EST	213256_at
clone 24707	/DB_XREF=gi:7281254	
mRNA sequence	/DB_XREF=est:hg41g06.x1	
	/CLONE=IMAGE:2948218 /UG=Hs.124969	
	Homo sapiens clone 24707 mRNA sequence	205467 -+
caspase 10,	gb:NM_001230.1 /DEF=Homo sapiens caspase	205467_at
apoptosis-related	10, apoptosis-related cysteine protease	
cysteine protease	(CASP10), mRNA. /FEA=mRNA	
	/GEN=CASP10 /PROD=caspase 10, apoptosis-	
	related cysteine protease /DB_XREF=gi:4502568	
	/UG=Hs.5353 caspase 10, apoptosis-related	
	cysteine protease /FL=gb:U60519.1	
	gb:NM_001230.1	216260
KIAA0690	Consensus includes gb:AK000238.1 /DEF=Homo	216360_x_at
protein	sapiens cDNA FLJ20231 fis, clone COLF5511,	
	highly similar to AB014590 Homo sapiens	
	mRNA for KIAA0690 protein. /FEA=mRNA	
l	/DB_XREF=gi:7020188 /UG=Hs.60103	
	KIAA0690 protein	227676_at
Homo sapiens,	Consensus includes gb:AW001287 /FEA=EST	227070_at
Similar to	/DB_XREF=gi:5848203	
RIKEN cDNA	/DB_XREF=est:wu27e06.x1	
1810037C20	/CLONE=IMAGE:2521282 /UG=Hs.61265	
gene, clone	ESTs, Weakly similar to G786_HUMAN	
MGC:21481	PROTEIN GS3786 H.sapiens	
IMAGE:385206		
2, mRNA,	· ·	
complete cds	Cincludes about A 581420 /FEA FST	244650_at
ESTs	Consensus includes gb:AA581439 /FEA=EST	277030_ai
	/DB_XREF=gi:2359211	
	/DB_XREF=est:nh13c10.s1 /CLONE=IMAGE:952242 /UG=Hs.152328	
	ESTs	
TOT	Consensus includes gb:AI739241 /FEA=EST	238984 at
ESTs	Consensus includes go:A1/37241 /FEA-E31	25070-1_at
	/DB_XREF=gi:5101222	
	/DB_XREF=est:wi14h02.x1 /CLONE=IMAGE:2390259 /UG=Hs.171480	
1	/CLONE=IMAGE:2390239 / 0G-Hs.171460 ESTs	
I		

11	C : 1 1 1 A DO ((010 1 /DED 1)	000000
hypothetical	Consensus includes gb:AB046810.1 /DEF=Homo	232083_at
protein	sapiens mRNA for KIAA1590 protein, partial	
FLJ23045	cds. /FEA=mRNA /GEN=KIAA1590	
	/PROD=KIAA1590 protein	
	/DB XREF=gi:10047254 /UG=Hs.101774	
	hypothetical protein FLJ23045	
regenerating	gb:AY007243.1 /DEF=Homo sapiens	222447 ot
		223447_at
gene type IV	regenerating gene type IV mRNA, complete cds.	
	/FEA=mRNA /PROD=regenerating gene type IV	
	/DB_XREF=gi:12621025 /UG=Hs.105484 Homo	
	sapiens regenerating gene type IV mRNA,	
	complete cds /FL=gb:AY007243.1	
ESTs	Consensus includes gb:AI139990 /FEA=EST	231022 at
	/DB XREF=gi:3647447	
	/DB XREF=est:qa47d03.x1	
i	/CLONE=IMAGE:1689893 /UG=Hs.134586	
EGT	ESTs	2250
ESTs	Consensus includes gb:AI733801 /FEA=EST	237923_at
<u> </u>	/DB_XREF=gi:5054914	
	/DB_XREF=est:qk39c04.x5	
1	/CLONE=IMAGE:1871334 /UG=Hs.146186	
	ESTs	A.
hypothetical	Consensus includes gb:AK002203.1 /DEF=Homo	226992 at
protein	sapiens cDNA FLJ11341 fis, clone	220772_at
MGC20702	PLACE1010786. /FEA=mRNA	
MGC20702		
	/DB_XREF=gi:7023932 /UG=Hs.10260 Homo	
	sapiens cDNA FLJ11341 fis, clone	
	PLACE1010786	
ESTs, Weakly	Consensus includes gb:AI457984 /FEA=EST	243729_at
similar to	/DB XREF=gi:4312002	_
ALU1 HUMAN	/DB XREF=est:tj66a04.x1	
ALU	/CLONE=IMAGE:2146446 /UG=Hs.165900	
SUBFAMILY J	ESTs, Weakly similar to ALUC HUMAN !!!!	
	_	
SEQUENCE	ALU CLASS C WARNING ENTRY !!!	
CONTAMINAT	H.sapiens	
ION WARNING		
ENTRY		
[H.sapiens]		
Homo sapiens	Consensus includes gb:T86159 /FEA=EST	227724 at
cDNA:	/DB XREF=gi:714511	· · · · · · · · · · · · · · · · · · ·
FLJ22063 fis,	/DB XREF=est:yd84h07.s1	
clone HEP10326	/CLONE=IMAGE:114973 /UG=Hs.10450	
cione fill 10520		
	Homo sapiens cDNA: FLJ22063 fis, clone	
	HEP10326	
ESTs	Consensus includes gb:AI806131 /FEA=EST	231148_at
	/DB_XREF=gi:5392697	
	/DB XREF=est:wf06c06.x1	
	/CLONE=IMAGE:2349802 /UG=Hs.99376	
	, 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	

	ESTs	
anterior gradient 2 (Xenepus laevis) homolog	Consensus includes gb:AI922323 /FEA=EST /DB_XREF=gi:5658287 /DB_XREF=est:wn90h03.x1 /CLONE=IMAGE:2453141 /UG=Hs.293380	228969_at
ESTs	ESTs Consensus includes gb:AI493909 /FEA=EST	235562 at
	/DB_XREF=gi:4394912 /DB_XREF=est:qz94e02.x1 /CLONE=IMAGE:2042234 /UG=Hs.6131_ESTs	_
hypothetical protein FLJ22233	Consensus includes gb:AI339568 /FEA=EST /DB_XREF=gi:4076495 /DB_XREF=est:qk67e10.x1 /CLONE=IMAGE:1874058 /UG=Hs.286194	222727_s_at
	hypothetical protein FLJ22233 /FL=gb:NM_024959.1	
GalNAc alpha-2, 6- sialyltransferase I, long form	Consensus includes gb:Y11339.2 /DEF=Homo sapiens mRNA for GalNAc alpha-2, 6-sialyltransferase I, long form. /FEA=mRNA /PROD=GalNAc alpha-2,6-sialyltransferase I /DB_XREF=gi:7576275 /UG=Hs.105352 GalNAc alpha-2, 6-sialyltransferase I, long form	227725_at
ESTs	Consensus includes gb:AI917390 /FEA=EST /DB_XREF=gi:5637245 /DB_XREF=est:ts79a05.x1 /CLONE=IMAGE:2237456 /UG=Hs.99415 ESTs	240964_at
Homo sapiens cDNA: FLJ22751 fis, clone KAIA0483, highly similar to AF016692 Homo sapiens small intestinal mucin (MUC3) mRNA	Consensus includes gb:AK026404.1 /DEF=Homo sapiens cDNA: FLJ22751 fis, clone KAIA0483, highly similar to AF016692 Homo sapiens small intestinal mucin (MUC3) mRNA. /FEA=mRNA /DB_XREF=gi:10439257 /UG=Hs.271819 Homo sapiens cDNA: FLJ22751 fis, clone KAIA0483, highly similar to AF016692 Homo sapiens small intestinal mucin (MUC3) mRNA	232321_at
Homo sapiens cDNA: FLJ23331 fis, clone HEP12664	Consensus includes gb:AK026984.1 /DEF=Homo sapiens cDNA: FLJ23331 fis, clone HEP12664. /FEA=mRNA /DB_XREF=gi:10439980 /UG=Hs.50742 Homo sapiens cDNA: FLJ23331 fis, clone HEP12664	229021_at
ESTs	Consensus includes gb:AA827649 /FEA=EST /DB_XREF=gi:2900090 /DB_XREF=est:od01a12.s1 /CLONE=IMAGE:1357918 /UG=Hs.105317 ESTs	235515_at
prostate cancer	Consensus includes gb:AA633076 /FEA=EST	226167_at

associated	/DD_VDEE-~:-2556400	
	/DB_XREF=gi:2556490	
protein 7	/DB_XREF=est:nq38a06.s1	
	/CLONE=IMAGE:1146130 /UG=Hs.27495	
FOR	prostate cancer associated protein 7	ļ
ESTs	Consensus includes gb:N37023 /FEA=EST	225407_at
	/DB_XREF=gi:1158165	
	/DB_XREF=est:yy40d03.s1	
	/CLONE=IMAGE:273701 /UG=Hs.235883	
	ESTs	
ESTs, Weakly	Consensus includes gb:AI864053 /FEA=EST	235678 at
similar to I38588	/DB_XREF=gi:5528160	
reverse	/DB XREF=est:wj55h10.x1	
transcriptase	/CLONE=IMAGE:2406787 /UG=Hs.39972	
homolog	ESTs, Weakly similar to I38588 reverse	
[H.sapiens]	transcriptase homolog H.sapiens	
ESTs, Weakly	Consensus includes gb:AA557324 /FEA=EST	227702 at
similar to	/DB_XREF=gi:2327801	227702_at
JX0331 laurate	/DB XREF=est:nl81a02.s1	
omega-	/CLONE=IMAGE:1057034 /UG=Hs.26040	
hydroxylase	ESTs, Weakly similar to fatty acid omega-	
[H.sapiens]	hydroxylase H.sapiens	
ESTs	Consensus includes gb:BF594323 /FEA=EST	229102 of
1019	/DB XREF=gi:11686647	238103_at
	/DB_XREF=g1.11080047 /DB_XREF=est:7h79g07.x1	
	/CLONE=IMAGE:3322236 /UG=Hs.158989 ESTs	
TOT- W-1-1-	<u> </u>	222241
ESTs, Weakly	Consensus includes gb:AI827789 /FEA=EST	228241_at
similar to	/DB_XREF=gi:5448449	
JE0350 Anterior	/DB_XREF=est:wf33a07.x1	
gradient-2	/CLONE=IMAGE:2357364 /UG=Hs.100686	
[H.sapiens]	ESTs, Weakly similar to JE0350 Anterior	
	gradient-2 H.sapiens	
ESTs	Consensus includes gb:AI968097 /FEA=EST	237835_at
<u> </u>	/DB_XREF=gi:5764915	
	/DB_XREF=est:wu13a12.x1	
	/CLONE=IMAGE:2516830 /UG=Hs.131360	
	ESTs	ł
ESTs	Consensus includes gb:H05025 /FEA=EST	241874 at
	/DB_XREF=gi:868577	_
	/DB_XREF=est:yl74g12.s1	
	/CLONE=IMAGE:43864 /UG=Hs.323767 ESTs	
Homo sapiens,	Consensus includes gb:AA524690 /FEA=EST	226168 at
Similar to	/DB XREF=gi:2265618	
RIKEN cDNA	/DB_XREF=est:ng38e07.s1	
1110060O18	/CLONE=IMAGE:937092 /UG=Hs.294143	
gene, clone	ESTs, Weakly similar to predicted using	
MGC:17236	Genefinder C.elegans	(
IMAGE:386413		
		L

7, mRNA, complete cds		
ESTs	Consensus includes gb:AI300126 /FEA=EST	240830 at
	/DB XREF=gi:3959472	_
	/DB_XREF=est:qn54f02.x1	
	/CLONE=IMAGE:1902075 /UG=Hs.257858	
	ESTs	
Homo sapiens	Consensus includes gb:AA129774 /FEA=EST	227019_at
cDNA FLJ13137	/DB_XREF=gi:1690185	
fis, clone	/DB_XREF=est:zl16h09.s1	
NT2RP3003150	/CLONE=IMAGE:502145 /UG=Hs.288905	
	Homo sapiens cDNA FLJ13137 fis, clone	
	NT2RP3003150	
ESTs	Consensus includes gb:AW024656 /FEA=EST	242358_at
	/DB_XREF=gi:5878186	
	/DB_XREF=est:wu78h05.x1	
	/CLONE=IMAGE:2526201 /UG=Hs.233382	
	ESTs, Moderately similar to AF119917 62	
	PRO2822 H.sapiens	

The biomarker probe set list B (Table 3) contains 95 probe sets (U133A: 47; U133B 48). The biomarker probe set list B contains polynucleotides identified to be biomarkers of EGFR antagonist sensitivity employing strategy B. In strategy B, polynucleotides were required to satisfy a stringent criteria for correlation to IC₅₀ values and a less stringent condition for EGFR status coregulation. Namely, the polynucleotides had to have a Pearsons correlation of -0.5 or less with respect to IC₅₀ and be called absent by the Affymetrix software in 5 out of the 6 cell lines with lowest expression of EGFR.

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TABLE 3 - Biomarker Probe Set List B

Unigene Title	Affymetrix Description	Affymetrix probe set
dopa decarboxylase (aromatic L- amino acid decarboxylase)	Consensus includes gb:AW772056 /FEA=EST /DB_XREF=gi:7704118 /DB_XREF=est:hn64g06.x1 /CLONE=IMAGE:3032698 /UG=Hs.150403 dopa decarboxylase (aromatic L-amino acid decarboxylase)	214347_s_at
cystic fibrosis transmembrane conductance regulator, ATP- binding cassette	gb:NM_000492.2 /DEF=Homo sapiens cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7) (CFTR), mRNA. /FEA=mRNA /GEN=CFTR /PROD=cystic fibrosis transmembrane	205043_at

(1, C '1 C		
(sub-family C,	conductanceregulator, ATP-binding cassette	
member 7)	(sub-family C, member 7)	
	/DB_XREF=gi:6995995 /UG=Hs.663 cystic	
	fibrosis transmembrane conductance regulator,	
	ATP-binding cassette (sub-family C, member 7)	
	/FL=gb:NM_000492.2	<u></u>
carcinoembryoni	gb:BC005008.1 /DEF=Homo sapiens,	203757_s_at
c antigen-related	carcinoembryonic antigen-related cell adhesion	
cell adhesion	molecule 6 (non-specific cross reacting antigen),	
molecule 6 (non-	clone MGC:10467, mRNA, complete cds.	
specific cross	/FEA=mRNA /PROD=carcinoembryonic	
reacting antigen)	antigen-related cell adhesionmolecule 6 (non-	
	specific cross reacting antigen)	
	/DB XREF=gi:13477106/UG=Hs.73848	
	carcinoembryonic antigen-related cell adhesion	
	molecule 6 (non-specific cross reacting antigen)	
	/FL=gb:BC005008.1 gb:M18216.1 gb:M29541.1	
	gb:NM 002483.1	
hypothetical	gb:NM 017655.1 /DEF=Homo sapiens	219970 at
protein	hypothetical protein FLJ20075 (FLJ20075),	217570_at
FLJ20075	mRNA./FEA=mRNA/GEN=FLJ20075	
TL320075	/PROD=hypothetical protein FLJ20075	
	/PROD=hypometical protein PE320073 /DB XREF=gi:8923083 /UG=Hs.205058	
	, -	
	hypothetical protein FLJ20075	
A TED C1.	/FL=gb:NM_017655.1	014070
ATPase, Class	Consensus includes gb:AW006935 /FEA=EST	214070_s_at
V, type 10B	/DB_XREF=gi:5855713	
	/DB_XREF=est:wt08b11.x1	
P	/CLONE=IMAGE:2506845 /UG=Hs.109358	
	ATPase, Class V, type 10B	
cystic fibrosis	Consensus includes gb:W60595 /FEA=EST	215702_s_at
transmembrane	/DB_XREF=gi:1367354	
conductance	/DB_XREF=est:zc91b04.s1	
regulator, ATP-	/CLONE=IMAGE:338479 /UG=Hs.663 cystic	
binding cassette	fibrosis transmembrane conductance regulator,	
(sub-family C,	ATP-binding cassette (sub-family C, member 7)	
member 7)		
HERV-H LTR-	gb:NM_007072.1 /DEF=Homo sapiens HERV-	220812_s_at
associating 2	H LTR-associating 2 (HHLA2), mRNA.	
	/FEA=mRNA /GEN=HHLA2 /PROD=HERV-H	
	LTR-associating 2 /DB_XREF=gi:5901963	
	/UG=Hs.252351 HERV-H LTR-associating 2	
	/FL=gb:AF126162.1 gb:NM_007072.1	
AA	Consensus includes gb:AV728958 /FEA=EST	212703 at
	/DB XREF=gi:10838379	
}	/DB XREF=est:AV728958	
	/CLONE=HTCBYF04 /UG=Hs.150443	
	KIAA0320 protein	
L	INTANOSZO PIORIII	L

1	Communication of management and management	014414
hemoglobin,	Consensus includes gb:T50399 /FEA=EST	214414_x_at
alpha 2	/DB_XREF=gi:652259	
	/DB_XREF=est:yb30b11.s1	
	/CLONE=IMAGE:72669 /UG=Hs.251577	
	hemoglobin, alpha 1	
spondin 1, (f-	Consensus includes gb:AI885290 /FEA=EST	213993_at
spondin)	/DB_XREF=gi:5590454	
extracellular	/DB_XREF=est:wl92a04.x1	
matrix protein	/CLONE=IMAGE:2432334 /UG=Hs.5378	
	spondin 1, (f-spondin) extracellular matrix	
	protein	
hemoglobin,	gb:BC005931.1 /DEF=Homo sapiens,	211745_x_at
alpha 1	hemoglobin, alpha 2, clone MGC:14541,	
	mRNA, complete cds. /FEA=mRNA	
	/PROD=hemoglobin, alpha 2	
	/DB_XREF=gi:13543547 /FL=gb:BC005931.1	
serine (or	gb:NM_002639.1 /DEF=Homo sapiens serine	204855 at
cysteine)	(or cysteine) proteinase inhibitor, clade B	_
proteinase	(ovalbumin), member 5 (SERPINB5), mRNA.	
inhibitor, clade B	/FEA=mRNA /GEN=SERPINB5 /PROD=serine	,
(ovalbumin),	(or cysteine) proteinase inhibitor, cladeB	
member 5	(ovalbumin), member 5 /DB XREF=gi:4505788	
	/UG=Hs.55279 serine (or cysteine) proteinase	
	inhibitor, clade B (ovalbumin), member 5	
	/FL=gb:NM_002639.1 gb:U04313.1	
3-hydroxy-3-	gb:NM 005518.1 /DEF=Homo sapiens 3-	204607 at
methylglutaryl-	hydroxy-3-methylglutaryl-Coenzyme A synthase	204007_at
Coenzyme A	2 (mitochondrial) (HMGCS2), mRNA.	
synthase 2	/FEA=mRNA/GEN=HMGCS2/PROD=3-	
(mitochondrial)	hydroxy-3-methylglutaryl-Coenzyme A synthase	
(intochondrial)	2(mitochondrial) /DB XREF=gi:5031750	
	/UG=Hs.59889 3-hydroxy-3-methylglutaryl-	
	Coenzyme A synthase 2 (mitochondrial)	
	/FL=gb:NM 005518.1	
enterior andient		200172 -+
anterior gradient 2 (Xenepus	gb:AF088867.1 /DEF=Homo sapiens putative secreted protein XAG mRNA, complete cds.	209173_at
laevis) homolog	1 *	
laevis) nomolog	/FEA=mRNA /PROD=putative secreted protein	
	XAG /DB_XREF=gi:6652811 /UG=Hs.91011	
	anterior gradient 2 (Xenepus laevis) homolog	
	/FL=gb:AF007791.1 gb:AF038451.1	
EXAM 4 .	gb:NM_006408.1 gb:AF088867.1	202402
FXYD domain-	gb:BC005238.1 /DEF=Homo sapiens, FXYD	202489_s_at
containing ion	domain-containing ion transport regulator 3,	
transport	clone MGC:12265, mRNA, complete cds.	
regulator 3	/FEA=mRNA /PROD=FXYD domain-	
	containing ion transport regulator3	
	/DB_XREF=gi:13528881 /UG=Hs.301350	
	FXYD domain-containing ion transport regulator	

	3 /FL=gb:NM_005971.2 gb:BC005238.1	
dipeptidylpeptida	gb:M80536.1 /DEF=H.sapiens dipeptidyl	203716 s at
se IV (CD26,	peptidase IV (DPP4) mRNA, complete cds.	203710_s_ai
adenosine	/FEA=mRNA /GEN=DPP4 /PROD=dipeptidyl	
deaminase		
	peptidase IV /DB_XREF=gi:181569	
complexing	/UG=Hs.44926 dipeptidylpeptidase IV (CD26,	
protein 2)	adenosine deaminase complexing protein 2)	
	/FL=gb:M80536.1 gb:NM 001935.1	215702
cystic fibrosis	Consensus includes gb:W60595 /FEA=EST	215703_at
transmembrane	/DB_XREF=gi:1367354	
conductance	/DB_XREF=est:zc91b04.s1	
regulator, ATP-	/CLONE=IMAGE:338479 /UG=Hs.663 cystic	
binding cassette	fibrosis transmembrane conductance regulator,	
(sub-family C,	ATP-binding cassette (sub-family C, member 7)	
member 7) ·		
EphA1	gb:NM_005232.1 /DEF=Homo sapiens EphA1	205977_s_at
	(EPHA1), mRNA. /FEA=mRNA /GEN=EPHA1	
	/PROD=EphA1 /DB_XREF=gi:4885208	
	/UG=Hs.89839 EphA1 /FL=gb:M18391.1	
	gb:NM 005232.1	
spondin 1, (f-	Consensus includes gb:AI885290 /FEA=EST	213994 s at
spondin)	/DB_XREF=gi:5590454	
extracellular	/DB XREF=est;wl92a04.x1	
matrix protein	/CLONE=IMAGE:2432334 /UG=Hs.5378	
mann protein	spondin 1, (f-spondin) extracellular matrix	
·	protein	Ì
CUG triplet	gb:NM 006561.1 /DEF=Homo sapiens CUG	202158_s_at
repeat, RNA-	triplet repeat, RNA-binding protein 2	202130_B_at
binding protein 2	(CUGBP2), mRNA. /FEA=mRNA	
oniding protein 2	/GEN=CUGBP2/PROD=CUG triplet repeat,	
	RNA-binding protein 2 /DB XREF=gi:5729815	
	/UG=Hs.211610 CUG triplet repeat, RNA-	
	binding protein 2 /FL=gb:U69546.1	
	gb:AF036956.1 gb:AF090694.1	
	gb:NM 006561.1	
DVE7D424C001	<u> </u>	215047
DKFZP434C091	Consensus includes gb:AL080170.1	215047_at
protein	/DEF=Homo sapiens mRNA; cDNA	
	DKFZp434C091 (from clone DKFZp434C091);	
	partial cds. /FEA=mRNA	
	/GEN=DKFZp434C091 /PROD=hypothetical	
	protein /DB_XREF=gi:5262639 /UG=Hs.51692	,
	DKFZP434C091 protein	
mucin 3B	Consensus includes gb:AF113616 /DEF=Homo	214676_x_at
	sapiens intestinal mucin 3 (MUC3) gene, partial	
	cds /FEA=mRNA /DB_XREF=gi:6466800	
)	/UG=Hs.129782 mucin 3A, intestinal	1
<u> </u>		
potassium	gb:U90065.1 /DEF=Human potassium channel	204678_s_at

		1
subfamily K,	/PROD=potassium channel KCNO1	
member 1	/DB_XREF=gi:1916294 /UG=Hs.79351	
(TWIK-1)	potassium channel, subfamily K, member 1	
	(TWIK-1)/FL=gb:U33632.1 gb:U90065.1	
	gb:U76996.1 gb:NM_002245.1	
nuclear receptor	gb:NM 000901.1 /DEF=Homo sapiens nuclear	205259_at
subfamily 3,	receptor subfamily 3, group C, member 2	_
group C, member	(NR3C2), mRNA. /FEA=mRNA /GEN=NR3C2	
$\begin{bmatrix} 2 & 1 \\ 2 & \end{bmatrix}$	/PROD=nuclear receptor subfamily 3, group C,	ļ
	member 2 /DB_XREF=gi:4505198	
	/UG=Hs.1790 nuclear receptor subfamily 3,	
	group C, member 2 /FL=gb:M16801.1	
	gb:NM 000901.1	
BTG family,	gb:NM 006763.1 /DEF=Homo sapiens BTG	201236 s at
member 2	family, member 2 (BTG2), mRNA.	
	/FEA=mRNA /GEN=BTG2 /PROD=BTG	
	family, member 2 /DB_XREF=gi:5802987	
	/UG=Hs.75462 BTG family, member 2	
	/FL=gb:U72649.1 gb:NM_006763.1	
G protein-	gb:AF062006.1 /DEF=Homo sapiens orphan G	210393_at
coupled receptor	protein-coupled receptor HG38 mRNA,	
49	complete cds. /FEA=mRNA /PROD=orphan G	
	protein-coupled receptor HG38	
	/DB_XREF=gi:3366801 /UG=Hs.285529 G	
	protein-coupled receptor 49 /FL=gb:AF062006.1	į
	gb:AF061444.1 gb:NM_003667.1	
hypothetical	gb:NM_017640.1 /DEF=Homo sapiens	219573_at
protein	hypothetical protein FLJ20048 (FLJ20048),	
FLJ20048	mRNA. /FEA=mRNA /GEN=FLJ20048	
	/PROD=hypothetical protein FLJ20048	
	/DB_XREF=gi:8923056 /UG=Hs.116470	
	hypothetical protein FLJ20048	
	/FL=gb:NM_017640.1	
cytochrome	gb:NM_000775.1 /DEF=Homo sapiens	205073_at
P450, subfamily	cytochrome P450, subfamily IIJ (arachidonic	
IIJ (arachidonic	acid epoxygenase) polypeptide 2 (CYP2J2),	
acid	mRNA. /FEA=mRNA /GEN=CYP2J2	
epoxygenase)	/PROD=cytochrome P450, subfamily IIJ	
polypeptide 2	(arachidonic acidepoxygenase) polypeptide 2	
	/DB_XREF=gi:4503226 /UG=Hs.152096	
	cytochrome P450, subfamily IIJ (arachidonic	
	acid epoxygenase) polypeptide 2	
	/FL=gb:U37143.1 gb:NM_000775.1	
brain-specific	gb:NM_007030.1 /DEF=Homo sapiens brain-	206179_s_at
protein p25 alpha	specific protein p25 alpha (p25), mRNA.	
	/FEA=mRNA /GEN=p25 /PROD=brain-specific	
	protein p25 alpha /DB_XREF=gi:5902017	
	/UG=Hs.29353 brain-specific protein p25 alpha	

	/FL=gb:AB017016.1 gb:NM 007030.1	
mucin 2,	gb:NM 002457.1 /DEF=Homo sapiens mucin 2,	204672 ==
intestinal/trachea		204673_at
1	intestinaltracheal (MUC2), mRNA.	
1	/FEA=mRNA /GEN=MUC2 /PROD=mucin 2,	
	intestinaltracheal /DB_XREF=gi:4505284	
·	/UG=Hs.315 mucin 2, intestinaltracheal	
	/FL=gb:NM_002457.1 gb:L21998.1	
hypothetical	gb:NM_017699.1 /DEF=Homo sapiens	219734_at
protein	hypothetical protein FLJ20174 (FLJ20174),	
FLJ20174	mRNA. /FEA=mRNA /GEN=FLJ20174	
	/PROD=hypothetical protein FLJ20174	
	/DB_XREF=gi:8923170 /UG=Hs.114556	+
	hypothetical protein FLJ20174	
	/FL=gb:NM_017699.1	
metastasis-	gb:NM_004739.1 /DEF=Homo sapiens	203444_s_at
associated 1-like	metastasis-associated 1-like 1 (MTA1L1),	
1	mRNA. /FEA=mRNA /GEN=MTA1L1	
	/PROD=metastasis-associated 1-like 1	
	/DB_XREF=gi:4758739 /UG=Hs.173043	
	metastasis-associated 1-like 1	
ļ	/FL=gb:AB016591.1 gb:NM 004739.1	
	gb:AF295807.1	
bone	gb:NM_001200.1 /DEF=Homo sapiens bone	205290 s at
morphogenetic	morphogenetic protein 2 (BMP2), mRNA.	
protein 2	/FEA=mRNA /GEN=BMP2 /PROD=bone	
_	morphogenetic protein 2 precursor	
	/DB XREF=gi:4557368 /UG=Hs.73853 bone	
	morphogenetic protein 2 /FL=gb:NM_001200.1	
heparanase	gb:NM_006665.1 /DEF=Homo sapiens	219403 s at
,	heparanase (HPSE), mRNA. /FEA=mRNA	
	/GEN=HPSE /PROD=heparanase	
	/DB_XREF=gi:5729872 /UG=Hs.44227	
	heparanase /FL=gb:AF165154.1 gb:AF152376.1	
	gb:NM 006665.1 gb:AF084467.1	
	gb:AF155510.1	
tumor necrosis	gb:BC002794.1 /DEF=Homo sapiens, tumor	209354 at
factor receptor	necrosis factor receptor superfamily, member 14	20735+_at
superfamily,	(herpesvirus entry mediator), clone MGC:3753,	
member 14	mRNA, complete cds. /FEA=mRNA	
(herpesvirus	/PROD=tumor necrosis factor receptor	
entry mediator)	superfamily, member 14 (herpesvirus entry	
oming moderatory	mediator) /DB XREF=gi:12803894	
	/UG=Hs.279899 tumor necrosis factor receptor	
	superfamily, member 14 (herpesvirus entry	
1	mediator) /FL=gb:BC002794.1 gb:U70321.1	
CUG triplet	gb:U81232.1 gb:NM 003820.1 gb:AF153978.1	202156
~	Consensus includes gb:N36839 /FEA=EST	202156_s_at
repeat, RNA-	/DB_XREF=gi:1157981	

binding protein 2	/DB_XREF=est:yy35f07.s1	
	/CLONE=IMAGE:273253 /UG=Hs.211610	
	CUG triplet repeat, RNA-binding protein 2	
	/FL=gb:U69546.1 gb:AF036956.1	
	gb:AF090694.1 gb:NM_006561.1	
ESTs,	Consensus includes gb:R06655 /FEA=EST	217546_at
Moderately	/DB_XREF=gi:757275	
similar to	/DB_XREF=est:yf10e02.r1	
AF078844 1	/CLONE=IMAGE:126458 /UG=Hs.188518	
hqp0376 protein	ESTs, Moderately similar to AF078844 1	
[H.sapiens]	hqp0376 protein H.sapiens	
hairless (mouse)	gb:NM_018411.1 /DEF=Homo sapiens hairless	220163_s_at
homolog	protein (putative single zinc finger transcription	
	factor protein, responsible for autosomal	
	recessive universal congenital alopecia, HR	
	gene) (HSA277165), mRNA. /FEA=mRNA	
	/GEN=HSA277165 /PROD=hairless protein	
	/DB XREF=gi:11036651 /UG=Hs.272367	
	hairless protein (putative single zinc finger	İ
	transcription factor protein, responsible for	
İ	autosomal recessive universal congenital	}
	alopecia, HR gene) /FL=gb:NM_018411.1	l
branched chain	Consensus includes gb:NM 005504.1	214452 at
aminotransferase	/DEF=Homo sapiens branched chain	_
1, cytosolic	aminotransferase 1, cytosolic (BCAT1), mRNA.	
-, -, -,	/FEA=CDS /GEN=BCAT1 /PROD=branched	
	chain aminotransferase 1, cytosolic	
	/DB XREF=gi:5031606/UG=Hs.157205	
	branched chain aminotransferase 1, cytosolic	
	/FL=gb:U21551.1 gb:NM_005504.1	
pancreas-	gb:NM 016341.1 /DEF=Homo sapiens	205112_at
enriched	pancreas-enriched phospholipase C	
phospholipase C	(LOC51196), mRNA. /FEA=mRNA	
	/GEN=LOC51196 /PROD=pancreas-enriched	
	phospholipase C /DB_XREF=gi:7705940	
	/UG=Hs.6733 pancreas-enriched phospholipase	
	C/FL=gb:AF190642.2 gb:AF117948.1	
	gb:NM 016341.1	
prostaglandin-	gb:NM 000963.1 /DEF=Homo sapiens	204748_at
	prostaglandin-endoperoxide synthase 2	
synthase 2	(prostaglandin GH synthase and	
1 -		
	/FEA=mRNA /GEN=PTGS2	
and	/PROD=prostaglandin-endoperoxide synthase	
J 1 2 2 3 8 2)		
	/UG=Hs.196384 prostaglandin-endoperoxide	
İ	synthase 2 (prostaglandin GH synthase and	1
(prostaglandin G/H synthase	prostaglandin-endoperoxide synthase 2 (prostaglandin GH synthase and cyclooxygenase) (PTGS2), mRNA. /FEA=mRNA /GEN=PTGS2 /PROD=prostaglandin-endoperoxide synthase 2(prostaglandin GH synthase and cyclooxygenase) /DB_XREF=gi:4506264 /UG=Hs.196384 prostaglandin-endoperoxide	204748_at

	cyclooxygenase) /FL=gb:M90100.1	
	gb:L15326.1 gb:NM_000963.1	
phosphatase and	gb:NM_000314.1 /DEF=Homo sapiens	204054_at
tensin homolog	phosphatase and tensin homolog (mutated in	
(mutated in	multiple advanced cancers 1) (PTEN), mRNA.	
multiple	/FEA=mRNA /GEN=PTEN	
advanced cancers	/PROD=phosphatase and tensin homolog	
1)	(mutated inmultiple advanced cancers 1)	
	/DB_XREF=gi:4506248 /UG=Hs.10712	
	phosphatase and tensin homolog (mutated in	
	multiple advanced cancers 1) /FL=gb:U92436.1	
	gb:U93051.1 gb:U96180.1 gb:NM_000314.1	201070
retinoic acid	Consensus includes gb:AI669229 /FEA=EST	221872_at
receptor	/DB_XREF=gi:4834003	
responder	/DB_XREF=est:wc13e06.x1	
(tazarotene	/CLONE=IMAGE:2315074 /UG=Hs.82547	
induced) 1	retinoic acid receptor responder (tazarotene	
	induced) 1	202601 -4
protease inhibitor	gb:NM_002638.1 /DEF=Homo sapiens protease	203691_at
3, skin-derived	inhibitor 3, skin-derived (SKALP) (PI3), mRNA.	
(SKALP)	/FEA=mRNA /GEN=PI3 /PROD=protease	
	inhibitor 3, skin-derived (SKALP)	
	/DB_XREF=gi:4505786 /UG=Hs.112341	
	protease inhibitor 3, skin-derived (SKALP)	
	/FL=gb:NM_002638.1 gb:NM_003438.1 /DEF=Homo sapiens zinc	207394 at
zinc finger	finger protein 137 (clone pHZ-30) (ZNF137),	207394_at
protein 137 (clone pHZ-30)	mRNA. /FEA=mRNA /GEN=ZNF137),	
(Clone priz-30)	/PROD=zinc finger protein 137 (clone pHZ-30)	
	/DB XREF=gi:4507988 /UG=Hs.151689 zinc	
	finger protein 137 (clone pHZ-30)	
	/FL=gb:NM 003438.1 gb:U09414.1	
myosin, light	gb:NM 002477.1 /DEF=Homo sapiens myosin,	205145 s at
polypeptide 5,	light polypeptide 5, regulatory (MYL5), mRNA.	#001.0_5_dt
regulatory	/FEA=mRNA/GEN=MYL5/PROD=myosin,	
	light polypeptide 5, regulatory	
	/DB XREF=gi:4505304 /UG=Hs.170482	
	myosin, light polypeptide 5, regulatory	:
	/FL=gb:L03785.1 gb:NM_002477.1	
tumor necrosis	gb:NM 000043.1 /DEF=Homo sapiens tumor	204781 s_at
factor receptor	necrosis factor receptor superfamily, member 6	
superfamily,	(TNFRSF6), mRNA. /FEA=mRNA	
member 6	/GEN=TNFRSF6 /PROD=apoptosis (APO-1)	
	antigen 1 /DB_XREF=gi:4507582	
	/UG=Hs.82359 tumor necrosis factor receptor	
	superfamily, member 6 /FL=gb:M67454.1	
	gb:NM_000043.1	
hypothetical	Consensus includes gb:AI339568 /FEA=EST	222727_s_at

		
protein	/DB_XREF=gi:4076495	
FLJ22233	/DB_XREF=est:qk67e10.x1	
	/CLONE=IMAGE:1874058 /UG=Hs.286194	
	hypothetical protein FLJ22233	
	/FL=gb:NM_024959.1	
regenerating	gb:AY007243.1 /DEF=Homo sapiens	223447_at
gene type IV	regenerating gene type IV mRNA, complete	
	cds. /FEA=mRNA /PROD=regenerating gene	
	type IV /DB XREF=gi:12621025	
	/UG=Hs.105484 Homo sapiens regenerating	
	gene type IV mRNA, complete cds	
	/FL=gb:AY007243.1	
Homo sapiens	Consensus includes gb:AK025615.1	225285 at
cDNA:	/DEF=Homo sapiens cDNA: FLJ21962 fis,	_
FLJ21962 fis,	clone HEP05564. /FEA=mRNA	
clone HEP05564	/DB XREF=gi:10438186 /UG=Hs.7567 Homo	
	sapiens cDNA: FLJ21962 fis, clone HEP05564	
phosphoprotein	Consensus includes gb:AK000680.1	225626 at
associated with	/DEF=Homo sapiens cDNA FLJ20673 fis,	
glycosphingolipi	clone KAIA4464. /FEA=mRNA	
d-enriched	/DB XREF=gi:7020924 /UG=Hs.266175	
microdomains	phosphoprotein associated with GEMs	
	/FL=gb:AF240634.1 gb:NM 018440.1	
hypothetical	Consensus includes gb:BF111925 /FEA=EST	226171 at
protein	/DB_XREF=gi:10941704	220171_4
FLJ20209	/DB_XREF=est:7138g05.x1	
11320207	/CLONE=IMAGE:3523784 /UG=Hs.3685	
	hypothetical protein FLJ20209	
Homo sapiens	Consensus includes gb:AA532640 /FEA=EST	226484 at
mRNA for	/DB XREF=gi:2276894	220404_41
KIAA1190	/DB XREF=est:nj17c04.s1	
protein, partial	/CLONE=IMAGE:986598 /UG=Hs.206259	
cds	Homo sapiens mRNA for KIAA1190 protein,	
cus	partial eds	
KIAA1543	Consensus includes gb:AB040976.1	226494 at
protein	/DEF=Homo sapiens mRNA for KIAA1543	220434_al
protein	protein, partial cds. /FEA=mRNA	
	/GEN=KIAA1543 /PROD=KIAA1543 protein	
	/DB XREF=gi:7959352 /UG=Hs.17686	1
	KIAA1543 protein	
hypothetical	Consensus includes gb:AW138767 /FEA=EST	227180 at
, - ~		22/100_ai
protein FLJ23563	/DB_XREF=gi:6143085 /DB_XREF=est:UI-H-	
FLJ23303	BI1-aep-a-12-0-UI.s1	
	/CLONE=IMAGE:2719799 /UG=Hs.274256	
DOT-	hypothetical protein FLJ23563	007200
ESTs	Consensus includes gb:AW264333 /FEA=EST	227320_at
	/DB_XREF=gi:6641075	
······································	/DB_XREF=est:xq98e01.x1	<u> </u>

	/CLONE=IMAGE:2758680 /UG=Hs.21835 ESTs	
ESTs	Consensus includes gb:BF589359 /FEA=EST /DB_XREF=gi:11681683 /DB_XREF=est:nab25d01.x1 /CLONE=IMAGE:3266737 /UG=Hs.13256 ESTs	227354_at
Homo sapiens, Similar to RIKEN cDNA 1810037C20 gene, clone MGC:21481 IMAGE:385206 2, mRNA, complete cds	Consensus includes gb:AW001287 /FEA=EST /DB_XREF=gi:5848203 /DB_XREF=est:wu27e06.x1 /CLONE=IMAGE:2521282 /UG=Hs.61265 ESTs, Weakly similar to G786_HUMAN PROTEIN GS3786 H.sapiens	227676_at
Homo sapiens cDNA: FLJ22063 fis, clone HEP10326	Consensus includes gb:T86159 /FEA=EST /DB_XREF=gi:714511 /DB_XREF=est:yd84h07.s1 /CLONE=IMAGE:114973 /UG=Hs.10450 Homo sapiens cDNA: FLJ22063 fis, clone HEP10326	227724_at
ESTs	Consensus includes gb:AI700341 /FEA=EST /DB_XREF=gi:4988241 /DB_XREF=est:wd06e10.x1 /CLONE=IMAGE:2327370 /UG=Hs.110406 ESTs	228653_at
ESTs	Consensus includes gb:BG494007 /FEA=EST /DB_XREF=gi:13455521 /DB_XREF=est:602542289F1 /CLONE=IMAGE:4673182 /UG=Hs.203213 ESTs	228716_at
ESTs	Consensus includes gb:AI559300 /FEA=EST /DB_XREF=gi:4509505 /DB_XREF=est:tq43d03.x1 /CLONE=IMAGE:2211557 /UG=Hs.294140 ESTs	229331_at
hypothetical protein	Consensus includes gb:AI830823 /FEA=EST /DB_XREF=gi:5451416 /DB_XREF=est:wj52b06.x1 /CLONE=IMAGE:2406419 /UG=Hs.95549 hypothetical protein	229439_s_at
ESTs	Consensus includes gb:BF431989 /FEA=EST /DB_XREF=gi:11444103 /DB_XREF=est:nab84a05.x1 /CLONE=IMAGE:3274280 /UG=Hs.203213 ESTs	229657_at
ESTs	Consensus includes gb:BF589413 /FEA=EST	229893_at

	/DD X/DET -: 11 (01727	
	/DB_XREF=gi:11681737	
	/DB_XREF=est:nab26b11.x1]
	/CLONE=IMAGE:3267020 /UG=Hs.55501	
	ESTs	
brain-specific	Consensus includes gb:BG055052 /FEA=EST	230104_s_at
protein p25 alpha	/DB XREF=gi:12512386	
	/DB XREF=est:nac94g06.x1	i
	/CLONE=IMAGE:3441995 /UG=Hs.29353	
	brain-specific protein p25 alpha	
ESTs, Weakly	Consensus includes gb:BF110588 /FEA=EST	230645 at
similar to	/DB XREF=gi:10940278	250045_at
MMHUE4	/DB_XREF=g1.10940278 /DB_XREF=est:7n39e12.x1	
	/CLONE=IMAGE:3567071 /UG=Hs.150478	
erythrocyte		ļ
membrane	ESTs, Weakly similar to KIAA0987 protein	
protein 4.1,	H.sapiens	:
parent splice		
form [H.sapiens]		
ESTs	Consensus includes gb:BF592062 /FEA=EST	230760_at
	/DB XREF=gi:11684386	
	/DB XREF=est:7n98h06.x1	
	/CLONE=IMAGE:3572962 /UG=Hs.233890	
	ESTs	
hepatocyte	Consensus includes gb:AI032108 /FEA=EST	230914 at
nuclear factor 4,	/DB XREF=gi:3250320	250514_ut
1	, = -	
alpha	/DB_XREF=est:ow92d11.x1	
İ	/CLONE=IMAGE:1654293 /UG=Hs.54424	
	hepatocyte nuclear factor 4, alpha	222244
ESTs	Consensus includes gb:AW203959 /FEA=EST	230944_at
	/DB_XREF=gi:6503431 /DB_XREF=est:UI-H-	
1	BI1-aeu-b-12-0-UI.s1	
	/CLONE=IMAGE:2720590 /UG=Hs.149532	
	ESTs	
ESTs	Consensus includes gb:AI139990 /FEA=EST	231022 at
	/DB XREF=gi:3647447	_
	/DB XREF=est:qa47d03.x1	
	/CLONE=IMAGE:1689893 /UG=Hs.134586	
	ESTs	
ESTs	Consensus includes gb:AI806131 /FEA=EST	231148 at
ESIS		251140_at
	/DB_XREF=gi:5392697	
	/DB_XREF=est:wf06c06.x1	
	/CLONE=IMAGE:2349802 /UG=Hs.99376	
	ESTs	
hypothetical	Consensus includes gb:AB046810.1	232083_at
protein	/DEF=Homo sapiens mRNA for KIAA1590	
FLJ23045	protein, partial cds. /FEA=mRNA	
	/GEN=KIAA1590 /PROD=KIAA1590 protein	
	/DB XREF=gi:10047254 /UG=Hs.101774	
	hypothetical protein FLJ23045	
	1 1 J P o di lo di la pio de la pione di l	

Homo sapiens	Consensus includes gb:AC004908 /DEF=Homo	232641 at
PAC clone RP5-	sapiens PAC clone RP5-855D21 /FEA=CDS 3	
855D21	/DB XREF=gi:4156179 /UG=Hs.249181	
	Homo sapiens PAC clone RP5-855D21	
putative	Consensus includes gb:AJ251708.1	234669 x at
microtubule-	/DEF=Homo sapiens partial mRNA for putative	
binding protein	microtubule-binding protein. /FEA=mRNA	
	/PROD=putative microtubule-binding protein	
	/DB XREF=gi:6491740 /UG=Hs.326544	
	putative microtubule-binding protein	
ESTs	Consensus includes gb:AI741469 /FEA=EST	234970 at
	/DB XREF=gi:5109757	
	/DB XREF=est:wg11b01.x1	
	/CLONE=IMAGE:2364745 /UG=Hs.57787	
	ESTs	
ESTs	Consensus includes gb:AI417897 /FEA=EST	235444 at
	/DB_XREF=gi:4261401	_
	/DB_XREF=est:tg55b06.x1	
	/CLONE=IMAGE:2112659 /UG=Hs.235860	
	ESTs	
ESTs	Consensus includes gb:AI493909 /FEA=EST	235562 at
	/DB_XREF=gi:4394912	_
	/DB_XREF=est:qz94e02.x1	
	/CLONE=IMAGE:2042234 /UG=Hs.6131	
	ESTs	
ESTs	Consensus includes gb:AV741130 /FEA=EST	235651_at
	/DB_XREF=gi:10858711	
	/DB_XREF=est:AV741130	
	/CLONE=CBCATB06/UG=Hs.173704 ESTs,	
	Moderately similar to ALU8_HUMAN ALU	
	SUBFAMILY SX SEQUENCE	,
	CONTAMINATION WARNING ENTRY	
	H.sapiens	
ESTs	Consensus includes gb:AW339510 /FEA=EST	235866_at
	/DB_XREF=gi:6836136	
	/DB_XREF=est:xz91h08.x1	
	/CLONE=IMAGE:2871615 /UG=Hs.42722	
	ESTs	
ESTs	Consensus includes gb:AI076192 /FEA=EST	236422_at
	/DB_XREF=gi:3405370	
	/DB_XREF=est:oz01g07.x1	
	/CLONE=IMAGE:1674108 /UG=Hs.131933	
	ESTs	
ESTs	Consensus includes gb:AL044570 /FEA=EST	236548_at
	/DB_XREF=gi:5432785	
	/DB_XREF=est:DKFZp434L082_s1	
	/CLONE=DKFZp434L082 /UG=Hs.147975	
	ESTs	

ESTs	Consensus includes gb:AI733801 /FEA=EST /DB_XREF=gi:5054914	237923_at
	/DB_XREF=est:qk39c04.x5 /CLONE=IMAGE:1871334 /UG=Hs.146186	
	ESTs : 1 1 TG0015 FEATEST	238422 at
Homo sapiens,	Consensus includes gb:T69015 /FEA=EST	236422_at
clone	/DB_XREF=gi:680163	
MGC:16402	/DB_XREF=est:yc31f04.s1	
IMAGE:394036	/CLONE=IMAGE:82303 /UG=Hs.192728	
0, mRNA,	ESTs	
complete cds		
ESTs	Consensus includes gb:AA502384 /FEA=EST	238956_at
	/DB_XREF=gi:2237351	
	/DB_XREF=est:ne27f11.s1	
	/CLONE=IMAGE:898605 /UG=Hs.151529	
	ESTs	
ESTs	Consensus includes gb:AI739241 /FEA=EST	238984_at
	/DB XREF=gi:5101222	
	/DB XREF=est:wi14h02.x1	
	/CLONE=IMAGE:2390259 /UG=Hs.171480	
	ESTs	
ESTs	Consensus includes gb:AA088446 /FEA=EST	239065_at
	/DB XREF=gi:1633958	
	/DB XREF=est:zl89f04.s1	
	/CLONE=IMAGE:511807 /UG=Hs.170298	
	ESTs	
ESTs	Consensus includes gb:AI493046 /FEA=EST	239148 at
DDIS	/DB XREF=gi:4394049	_
	/DB XREF=est:qz49b04.x1	
	/CLONE=IMAGE:2030191 /UG=Hs.146133	
ļ.	ESTs	
ESTs	Consensus includes gb:AI243098 /FEA=EST	239966 at
LDIS	/DB XREF=gi:3838495	_
	/DB XREF=est:qh26e03.x1	
	/CLONE=IMAGE:1845820 /UG=Hs.178398	
	ESTs	
ESTs, Weakly	Consensus includes gb:AI633523 /FEA=EST	240106 at
similar to	/DB XREF=gi:4684853	
A49175 Motch B	/DB_XREF=gt.4004633 /DB_XREF=est:th68b11.x1	
	/CLONE=IMAGE:2123805 /UG=Hs.44705	
protein - mouse	ESTs	
[M.musculus]	Consensus includes gb:AI620677 /FEA=EST	241412 at
betacellulin		211712_at
	/DB_XREF=gi:4629803	
	/DB_XREF=est:tu85e09.x1	
	/CLONE=IMAGE:2257864 /UG=Hs.154191	
	ESTs - L L DECOCOLC/FEA - EST	242626 at
ESTs	Consensus includes gb:BF696216 /FEA=EST	242626_at
	/DB_XREF=gi:11981624	

	/DB_XREF=est:602124536F1 /CLONE=IMAGE:4281632 /UG=Hs.188724 ESTs	
ESTs	Consensus includes gb:N57929 /FEA=EST /DB_XREF=gi:1201819 /DB_XREF=est:yv61e06.s1 /CLONE=IMAGE:247234 /UG=Hs.48100 ESTs	242978_x_at
ESTs, Weakly similar to ALU1_HUMAN ALU SUBFAMILY J SEQUENCE CONTAMINAT ION WARNING ENTRY [H.sapiens]	Consensus includes gb:AI457984 /FEA=EST /DB_XREF=gi:4312002 /DB_XREF=est:tj66a04.x1 /CLONE=IMAGE:2146446 /UG=Hs.165900 ESTs, Weakly similar to ALUC_HUMAN !!!! ALU CLASS C WARNING ENTRY !!! H.sapiens	243729_at
ESTs	Consensus includes gb:AA581439 /FEA=EST /DB_XREF=gi:2359211 /DB_XREF=est:nh13c10.s1 /CLONE=IMAGE:952242 /UG=Hs.152328 ESTs	244650_at

The two biomarker probe sets A and B were then combined, a total of 161 different probe sets, and the redundant polynucleotides were removed, representing 125 unique polynucleotides which are provided below in Table 4. The Table 4 polynucleotides are biomarkers of the invention.

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TABLE 4 - Biomarkers

Unigene Title	Affymetrix Description	Affymetrix
And SEQ ID NO:		probe set
3-hydroxy-3-	gb:NM_005518.1 /DEF=Homo sapiens 3-	204607 at
methylglutaryl-	hydroxy-3-methylglutaryl-Coenzyme A	_
Coenzyme A	synthase 2 (mitochondrial) (HMGCS2),	
synthase 2	mRNA. /FEA=mRNA /GEN=HMGCS2	
(mitochondrial)	/PROD=3-hydroxy-3-methylglutaryl-	
}	Coenzyme A synthase 2(mitochondrial)	
SEQ ID NOS: 1	/DB_XREF=gi:5031750 /UG=Hs.59889 3-	
(DNA) and 126	hydroxy-3-methylglutaryl-Coenzyme A	
(amino acid)	synthase 2 (mitochondrial)	
	/FL=gb:NM_005518.1	ļ
ATPase, Class V,	Consensus includes gb:AW006935	214070_s at
type 10B	/FEA=EST/DB_XREF=gi:5855713	
	/DB_XREF=est:wt08b11.x1	

SEQ ID NO: 2	/CLONE=IMAGE:2506845 /UG=Hs.109358	
(DNA)	ATPase, Class V, type 10B	
bone morphogenetic	gb:NM 001200.1 /DEF=Homo sapiens bone	205290 s at
	morphogenetic protein 2 (BMP2), mRNA.	203270_5_4
protein 2	/FEA=mRNA /GEN=BMP2 /PROD=bone	
GEO ID MOG. 2	morphogenetic protein 2 precursor	
SEQ ID NOS: 3		
(DNA) and 127	/DB_XREF=gi:4557368 /UG=Hs.73853 bone	
(amino acid)	morphogenetic protein 2	
	/FL=gb:NM_001200.1	206170+
brain-specific protein	gb:NM_007030.1 /DEF=Homo sapiens brain-	206179_s_at
p25 alpha	specific protein p25 alpha (p25), mRNA.	
	/FEA=mRNA /GEN=p25 /PROD=brain-	
SEQ ID NOS: 4	specific protein p25 alpha	
(DNA) and 128	/DB_XREF=gi:5902017 /UG=Hs.29353	
(amino acid)	brain-specific protein p25 alpha	
	/FL=gb:AB017016.1 gb:NM_007030.1	
branched chain	Consensus includes gb:NM_005504.1	214452_at
aminotransferase 1,	/DEF=Homo sapiens branched chain	
cytosolic	aminotransferase 1, cytosolic (BCAT1),	
	mRNA. /FEA=CDS /GEN=BCAT1	
SEQ ID NOS: 5	/PROD=branched chain aminotransferase 1,	
(DNA) and 129	cytosolic /DB XREF=gi:5031606	
(amino acid)	/UG=Hs.157205 branched chain	
	aminotransferase 1, cytosolic	
	/FL=gb:U21551.1 gb:NM_005504.1	
BTG family, member	gb:NM 006763.1 /DEF=Homo sapiens BTG	201236 s at
2	family, member 2 (BTG2), mRNA.	
	/FEA=mRNA /GEN=BTG2 /PROD=BTG	
SEQ ID NOS: 6	family, member 2 /DB_XREF=gi:5802987	
(DNA) and 130	/UG=Hs.75462 BTG family, member 2	i I
(amino acid)	/FL=gb:U72649.1 gb:NM_006763.1	
Carcinoembryonic	gb:BC005008.1 /DEF=Homo sapiens,	203757 s at
antigen-related cell	carcinoembryonic antigen-related cell	1 200,0,0,0
adhesion molecule 6	adhesion molecule 6 (non-specific cross	
	reacting antigen), clone MGC:10467, mRNA,	
(non-specific cross	complete cds. /FEA=mRNA	
reacting antigen)	/PROD=carcinoembryonic antigen-related	
GEO ID MOG. 7	cell adhesionmolecule 6 (non-specific cross	
SEQ ID NOS: 7		
(DNA) and 131	reacting antigen) /DB_XREF=gi:13477106	
(amino acid)	/UG=Hs.73848 carcinoembryonic antigen-	
	related cell adhesion molecule 6 (non-specific	
	cross reacting antigen) /FL=gb:BC005008.1	
	gb:M18216.1 gb:M29541.1 gb:NM_002483.1	205467
caspase 10, apoptosis-	gb:NM_001230.1 /DEF=Homo sapiens	205467_at
related cysteine	caspase 10, apoptosis-related cysteine	
protease	protease (CASP10), mRNA. /FEA=mRNA	
	/GEN=CASP10 /PROD=caspase 10,	
SEQ ID NOS: 8	apoptosis-related cysteine protease	

/DB_XREF=oi:4502568/UG=Hs 5353	T
,	
	202158 s at
•	202136_S_at
,	
1	206994_at
1 5	
	205043_at
l	
1 = ' ' ' '	
/FEA=mRNA/GEN=CFTR/PROD=cystic	
fibrosis transmembrane conductanceregulator,	
ATP-binding cassette (sub-family C, member	
7) /DB_XREF=gi:6995995 /UG=Hs.663	ļ
cystic fibrosis transmembrane conductance	
regulator, ATP-binding cassette (sub-family	
C, member 7) /FL=gb:NM_000492.2	
gb:NM_000775.1 /DEF=Homo sapiens	205073_at
cytochrome P450, subfamily IIJ (arachidonic	
acid epoxygenase) polypeptide 2 (CYP2J2),	
mRNA. /FEA=mRNA /GEN=CYP2J2	
/PROD=cytochrome P450, subfamily IIJ	
(arachidonic acidepoxygenase) polypeptide 2	
/DB_XREF=gi:4503226 /UG=Hs.152096	
cytochrome P450, subfamily IIJ (arachidonic	
acid epoxygenase) polypeptide 2	
/FL=gb:U37143.1 gb:NM_000775.1	
gb:M80536.1 /DEF=H.sapiens dipeptidyl	203716_s_at
peptidase IV (DPP4) mRNA, complete cds.	
/FEA=mRNA /GEN=DPP4	
/PROD=dipeptidyl peptidase IV	
/DB_XREF=gi:181569 /UG=Hs.44926	
dipeptidylpeptidase IV (CD26, adenosine	
deaminase complexing protein 2)	
/FL=gb:M80536.1 gb:NM_001935.1	
Consensus includes gb:AL080170.1	215047 at
/DEF=Homo sapiens mRNA; cDNA	_
	ATP-binding cassette (sub-family C, member 7) /DB_XREF=gi:6995995 /UG=Hs.663 cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7) /FL=gb:NM_000492.2 gb:NM_000775.1 /DEF=Homo sapiens cytochrome P450, subfamily IIJ (arachidonic acid epoxygenase) polypeptide 2 (CYP2J2), mRNA. /FEA=mRNA /GEN=CYP2J2 /PROD=cytochrome P450, subfamily IIJ (arachidonic acidepoxygenase) polypeptide 2 /DB_XREF=gi:4503226 /UG=Hs.152096 cytochrome P450, subfamily IIJ (arachidonic acid epoxygenase) polypeptide 2 /FL=gb:U37143.1 gb:NM_000775.1 gb:M80536.1 /DEF=H.sapiens dipeptidyl peptidase IV (DPP4) mRNA, complete cds. /FEA=mRNA /GEN=DPP4 /PROD=dipeptidyl peptidase IV (CD26, adenosine deaminase complexing protein 2) /FL=gb:M80536.1 gb:NM_001935.1 Consensus includes gb:AL080170.1

• •	
	014047
	214347_s_at
gb:NM_005232.1 /DEF=Homo sapiens	205977_s_at
-	
. •	217546_at
/DB_XREF=gi:757275	
/DB_XREF=est:yf10e02.r1	:
/CLONE=IMAGE:126458 /UG=Hs.188518	
ESTs, Moderately similar to AF078844 1	
hqp0376 protein H.sapiens	
Consensus includes gb:AW675655	222354_at
/FEA=EST /DB_XREF=gi:7540890	
/DB_XREF=est:ba52e01.x1	
/CLONE=IMAGE:2900184 /UG=Hs.314158	
ESTs	
gb:NM_022969.1 /DEF=Homo sapiens	203638_s_at
fibroblast growth factor receptor 2 (bacteria-	
expressed kinase, keratinocyte growth factor	
receptor, craniofacial dysostosis 1, Crouzon	1
syndrome, Pfeiffer syndrome, Jackson-Weiss	
syndrome) (FGFR2), transcript variant 2,	
mRNA. /FEA=mRNA /GEN=FGFR2	
/PROD=fibroblast growth factor receptor 2,	
isoform 2precursor /DB_XREF=gi:13186252	
/UG=Hs.278581 fibroblast growth factor	
receptor 2 (bacteria-expressed kinase,	
keratinocyte growth factor receptor,	
craniofacial dysostosis 1, Crouzon syndrome,	
Pfeiffer syndrome, Jackson-Weiss syndrome)	
/FL=gb:NM_022969.1 gb:M97193.1	
gb:M80634.1	
gb:BC005238.1 /DEF=Homo sapiens, FXYD	202489_s_at
domain-containing ion transport regulator 3,	
	/CLONE=IMAGE:126458 /UG=Hs.188518 ESTs, Moderately similar to AF078844 1 hqp0376 protein H.sapiens Consensus includes gb:AW675655 /FEA=EST /DB_XREF=gi:7540890 /DB_XREF=est:ba52e01.x1 /CLONE=IMAGE:2900184 /UG=Hs.314158 ESTs gb:NM_022969.1 /DEF=Homo sapiens fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome) (FGFR2), transcript variant 2, mRNA. /FEA=mRNA /GEN=FGFR2 /PROD=fibroblast growth factor receptor 2, isoform 2precursor /DB_XREF=gi:13186252 /UG=Hs.278581 fibroblast growth factor receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome) /FL=gb:NM_022969.1 gb:M97193.1 gb:M80634.1 gb:BC005238.1 /DEF=Homo sapiens, FXYD

transport regulator 3	clone MGC:12265, mRNA, complete cds.	
	/FEA=mRNA /PROD=FXYD domain-	
SEQ ID NOS: 20	containing ion transport regulator3	
(DNA) and 140	/DB_XREF=gi:13528881 /UG=Hs.301350	
(amino acid)	FXYD domain-containing ion transport	
	regulator 3 /FL=gb:NM_005971.2	
	gb:BC005238.1	210202 ot
G protein-coupled	gb:AF062006.1 /DEF=Homo sapiens orphan	210393_at
receptor 49	G protein-coupled receptor HG38 mRNA,	
	complete cds. /FEA=mRNA /PROD=orphan	
SEQ ID NOS: 21	G protein-coupled receptor HG38	
(DNA) and 141	/DB_XREF=gi:3366801 /UG=Hs.285529 G	
(amino acid)	protein-coupled receptor 49	
	/FL=gb:AF062006.1 gb:AF061444.1	
	gb:NM 003667.1	220163 s at
hairless (mouse)	gb:NM_018411.1 /DEF=Homo sapiens	220103_8_at
homolog	hairless protein (putative single zinc finger	
	transcription factor protein, responsible for	
SEQ ID NOS: 22	autosomal recessive universal congenital	
(DNA) and 142	alopecia, HR gene) (HSA277165), mRNA.	
(amino acid)	/FEA=mRNA /GEN=HSA277165	
	/PROD=hairless protein	
	/DB_XREF=gi:11036651 /UG=Hs.272367	
	hairless protein (putative single zinc finger	
	transcription factor protein, responsible for	
	autosomal recessive universal congenital	
	alopecia, HR gene) /FL=gb:NM_018411.1 gb:BC005931.1 /DEF=Homo sapiens,	211745 x at
hemoglobin, alpha 1	hemoglobin, alpha 2, clone MGC:14541,	211745_A_at
GEO ID MOG 22	mRNA, complete cds. /FEA=mRNA	
SEQ ID NOS: 23		
(DNA) and 143	/PROD=hemoglobin, alpha 2	
(amino acid)	/DB_XREF=gi:13543547	
1 11: 1-1-2	/FL=gb:BC005931.1 Consensus includes gb:T50399 /FEA=EST	214414_x_at
hemoglobin, alpha 2	/DB XREF=gi:652259	211111_X_40
GEO ID NO. 24	/DB_XREF=est:yb30b11.s1	*
SEQ ID NO: 24	/CLONE=IMAGE:72669 /UG=Hs.251577	
(DNA)	hemoglobin, alpha 1	
1	gb:NM 006665.1 /DEF=Homo sapiens	219403 s at
heparanase	heparanase (HPSE), mRNA. /FEA=mRNA	219 103_5_44
GEO ID MOG. 25	/GEN=HPSE /PROD=heparanase	
SEQ ID NOS: 25	/GEN=HFSE/FROD=heparanasc /DB_XREF=gi:5729872/UG=Hs.44227	
(DNA) and 144	heparanase /FL=gb:AF165154.1	
(amino acid)	gb:AF152376.1 gb:NM_006665.1	
	gb:AF132376.1 gb:AWI_000003.1 gb:AF084467.1 gb:AF155510.1	
II.	Consensus includes gb:AL022313	217354 s at
Hermansky-Pudlak	/DEF=Human DNA sequence from clone	#1155 1_0_ac
syndrome	RP5-1119A7 on chromosome 22q12.2-12.3	
	Kt J=1119/x/ Off CHIOIHOSOHIC 22412.2-12.5	

GEO ID NOG. 26	Contains the TVND save for mitachandrial	
SEQ ID NOS: 26	Contains the TXN2 gene for mitochondrial	
(DNA) and 145	thioredoxin, a novel gene, the EIF3S7 gene	
(amino acid)	for eukaryotic translation initiation factor 3	
	subunit 7 (zeta, 6667kD) (EIF3-P66), the	
	gene f /FEA=CDS_3	
	/DB_XREF=gi:4200326 /UG=Hs.272270	İ
	Human DNA sequence from clone RP5-	
	1119A7 on chromosome 22q12.2-12.3	
1	Contains the TXN2 gene for mitochondrial	
	thioredoxin, a novel gene, the EIF3S7 gene	
	for eukaryotic translation initiation factor 3	
1	subunit 7 (zeta, 6667kD) (EIF3-P66), the	
	gene for a nov	1
HERV-H LTR-	gb:NM_007072.1 /DEF=Homo sapiens	220812_s_at
associating 2	HERV-H LTR-associating 2 (HHLA2),	
	mRNA. /FEA=mRNA /GEN=HHLA2	
SEQ ID NOS: 27	/PROD=HERV-H LTR-associating 2	
(DNA) and 146	/DB_XREF=gi:5901963 /UG=Hs.252351	
(amino acid)	HERV-H LTR-associating 2	
	/FL=gb:AF126162.1 gb:NM_007072.1	
Homo sapiens clone	Consensus includes gb:AW593996	213256_at
24707 mRNA	/FEA=EST/DB_XREF=gi:7281254	
sequence	/DB_XREF=est:hg41g06.x1	
	/CLONE=IMAGE:2948218 /UG=Hs.124969	
SEQ ID NO: 28	Homo sapiens clone 24707 mRNA sequence	
(DNA)		
Homo sapiens	Consensus includes gb:AL049983.1	217288_at
mRNA; cDNA	/DEF=Homo sapiens mRNA; cDNA	
DKFZp564D042	DKFZp564D042 (from clone	
(from clone	DKFZp564D042). /FEA=mRNA	
DKFZp564D042)	/DB_XREF=gi:4884234 /UG=Hs.240136	
	Homo sapiens mRNA; cDNA	
SEQ ID NO: 29	DKFZp564D042 (from clone	
(DNA)	DKFZp564D042)	
hypothetical protein	gb:NM 017640.1 /DEF=Homo sapiens	219573_at
FLJ20048	hypothetical protein FLJ20048 (FLJ20048),	
	mRNA. /FEA=mRNA /GEN=FLJ20048	
SEQ ID NOS: 30	/PROD=hypothetical protein FLJ20048	
(DNA) and 147	/DB_XREF=gi:8923056 /UG=Hs.116470	
(amino acid)	hypothetical protein FLJ20048	
	/FL=gb:NM_017640.1	
hypothetical protein	gb:NM_017655.1 /DEF=Homo sapiens	219970_at
FLJ20075	hypothetical protein FLJ20075 (FLJ20075),	-
	mRNA. /FEA=mRNA /GEN=FLJ20075	
SEQ ID NOS: 31	/PROD=hypothetical protein FLJ20075	
(DNA) and 148	/DB XREF=gi:8923083 /UG=Hs.205058	1
(amino acid)	hypothetical protein FLJ20075	
	/FL=gb:NM 017655.1	
	1 · · · · · · · · · · · · · · · · · · ·	

interferon consensus	Consensus includes gb:AI073984 /FEA=EST	204057 at
sequence binding	/DB XREF=gi:3400628	
protein 1	/DB XREF=est:oy66c05.x1	
protein	/CLONE=IMAGE:1670792 /UG=Hs.14453	
SEQ ID NO: 32	interferon consensus sequence binding protein	
(DNA)	1/FL=gb:M91196.1 gb:NM_002163.1	
KIAA0690 protein	Consensus includes gb:AK000238.1	216360 x at
Ki-A-10090 protein	/DEF=Homo sapiens cDNA FLJ20231 fis,	210500_x_at
SEQ ID NO: 33	clone COLF5511, highly similar to	
(DNA)	AB014590 Homo sapiens mRNA for	
(DIVA)	KIAA0690 protein. /FEA=mRNA	
	/DB XREF=gi:7020188 /UG=Hs.60103	
	KIAA0690 protein	
matrilin 3	gb:NM 002381.2 /DEF=Homo sapiens	206091 at
maumm 5	matrilin 3 (MATN3) precursor, mRNA.	200091_ai
SEO ID NOS. 24	/FEA=mRNA /GEN=MATN3	
SEQ ID NOS: 34		
(DNA) and 149	/PROD=matrilin 3 precursor	
(amino acid)	/DB_XREF=gi:13518040 /UG=Hs.278461	
	matrilin 3 /FL=gb:NM_002381.2	202444+
metastasis-associated	gb:NM_004739.1 /DEF=Homo sapiens	203444_s_at
1-like 1	metastasis-associated 1-like 1 (MTA1L1),	
GEO ID NOG 25	mRNA. /FEA=mRNA /GEN=MTA1L1	
SEQ ID NOS: 35	/PROD=metastasis-associated 1-like 1	
(DNA) and 150	/DB_XREF=gi:4758739 /UG=Hs.173043	
(amino acid)	metastasis-associated 1-like 1	
	/FL=gb:AB016591.1 gb:NM_004739.1	
	gb:AF295807.1	204672
mucin 2,	gb:NM_002457.1 /DEF=Homo sapiens mucin	204673_at
intestinal/tracheal	2, intestinaltracheal (MUC2), mRNA.	
	/FEA=mRNA /GEN=MUC2 /PROD=mucin	
SEQ ID NOS: 36	2, intestinaltracheal /DB_XREF=gi:4505284	
(DNA) and 151	/UG=Hs.315 mucin 2, intestinaltracheal	
(amino acid)	/FL=gb:NM_002457.1 gb:L21998.1	
mucin 3B	Consensus includes gb:AB038783.1	214898_x_at
	/DEF=Homo sapiens MUC3B mRNA for	
SEQ ID NOS: 37	intestinal mucin, partial cds. /FEA=mRNA	
(DNA) and 152	/GEN=MUC3B /PROD=intestinal mucin	
(amino acid)	/DB_XREF=gi:9929917 /UG=Hs.129782	
	mucin 3A, intestinal	
myosin, heavy	gb:NM_003802.1 /DEF=Homo sapiens	208208_at
polypeptide 13,	myosin, heavy polypeptide 13, skeletal	
skeletal muscle	muscle (MYH13), mRNA. /FEA=mRNA	
	/GEN=MYH13 /PROD=myosin, heavy	
SEQ ID NOS: 38	polypeptide 13, skeletal muscle	
(DNA) and 153	/DB_XREF=gi:11321578 /UG=Hs.278488	
(amino acid)	myosin, heavy polypeptide 13, skeletal	
	muscle /FL=gb:NM_003802.1	
	gb:AF111782.2	

1:-1-4	-1-NIM 002477 1 /DEE TT	005145
myosin, light	gb:NM_002477.1 /DEF=Homo sapiens	205145_s_at
polypeptide 5,	myosin, light polypeptide 5, regulatory	
regulatory	(MYL5), mRNA. /FEA=mRNA	
	/GEN=MYL5 /PROD=myosin, light	
SEQ ID NOS: 39	polypeptide 5, regulatory	
(DNA) and 154	/DB_XREF=gi:4505304 /UG=Hs.170482	
(amino acid)	myosin, light polypeptide 5, regulatory	ļ
	/FL=gb:L03785.1 gb:NM_002477.1	
nuclear receptor	gb:NM 000901.1 /DEF=Homo sapiens	205259 at
subfamily 3, group C,	nuclear receptor subfamily 3, group C,	1 200 20 3 _ 440
member 2	member 2 (NR3C2), mRNA. /FEA=mRNA	
	/GEN=NR3C2 /PROD=nuclear receptor	
SEQ ID NOS: 40	subfamily 3, group C, member 2	
(DNA) and 155	/DB XREF=gi:4505198 /UG=Hs.1790	
(amino acid)	, = •	
(amino acid)	nuclear receptor subfamily 3, group C,	
	member 2 /FL=gb:M16801.1	
1	gb:NM_000901.1	
nuclear receptor	Consensus includes gb:AF228413.1	210174_at
subfamily 5, group A,	/DEF=Homo sapiens hepatocyte transcription	
member 2	factor mRNA, 3UTR. /FEA=mRNA	
	/DB_XREF=gi:7677372 /UG=Hs.183123	
SEQ ID NOS: 41	nuclear receptor subfamily 5, group A,	
(DNA) and 156	member 2 /FL=gb:U93553.1 gb:AB019246.1	
(amino acid)	gb:AF124247.1	
pancreas-enriched	gb:NM_016341.1 /DEF=Homo sapiens	205112_at
phospholipase C	pancreas-enriched phospholipase C	
	(LOC51196), mRNA. /FEA=mRNA	
SEQ ID NOS: 42	/GEN=LOC51196 /PROD=pancreas-enriched	
(DNA) and 157	phospholipase C /DB XREF=gi:7705940	
(amino acid)	/UG=Hs.6733 pancreas-enriched	
	phospholipase C /FL=gb:AF190642.2	
	gb:AF117948.1 gb:NM 016341.1	
peroxisomal trans 2-	gb:NM 018441.1 /DEF=Homo sapiens	221142 s at
enoyl CoA reductase;	peroxisomal trans 2-enoyl CoA reductase;	
putative short chain	putative short chain alcohol dehydrogenase	
alcohol	(HSA250303), mRNA. /FEA=mRNA	
dehydrogenase	/GEN=HSA250303 /PROD=peroxisomal	
dellydrogenase	trans 2-enoyl CoA reductase; putative short	
SEO ID NOS. 42		,
SEQ ID NOS: 43	chain alcohol dehydrogenase	
(DNA) and 158	/DB_XREF=gi:8923751 /UG=Hs.281680	
(amino acid)	peroxisomal trans 2-enoyl CoA reductase;	
İ	putative short chain alcohol dehydrogenase	
1	/FL=gb:NM_018441.1	
phosducin	gb:M33478.1 /DEF=Human 33-kDa	211496_s_at
	phototransducing protein mRNA, complete	
SEQ ID NOS: 44	cds. /FEA=mRNA /DB_XREF=gi:177186	
(DNA) and 159	/UG=Hs.550 phosducin	· ·
(amino acid)	/FL=gb:NM 022577.1 gb:M33478.1	

	gb:AF076465.1	
phosphatase and	gb:NM 000314.1 /DEF=Homo sapiens	204054 at
tensin homolog	phosphatase and tensin homolog (mutated in	201031_46
(mutated in multiple	multiple advanced cancers 1) (PTEN),	
advanced cancers 1)	mRNA. /FEA=mRNA /GEN=PTEN	
advanced cancers 1)	/PROD=phosphatase and tensin homolog	
SEQ ID NOS: 45	(mutated inmultiple advanced cancers 1)	
(DNA) and 160	/DB_XREF=gi:4506248 /UG=Hs.10712	
(amino acid)	phosphatase and tensin homolog (mutated in	
(animo acid)	multiple advanced cancers 1)	
	· · · · · · · · · · · · · · · · · · ·	
	/FL=gb:U92436.1 gb:U93051.1 gb:U96180.1	
	gb:NM 000314.1	204670
potassium channel,	gb:U90065.1 /DEF=Human potassium	204678_s_at
subfamily K, member	channel KCNO1 mRNA, complete cds.	
1 (TWIK-1)	/FEA=mRNA /PROD=potassium channel	
GT0 T 170G 46	KCNO1 /DB_XREF=gi:1916294	
SEQ ID NOS: 46	/UG=Hs.79351 potassium channel, subfamily	
(DNA) and 161	K, member 1 (TWIK-1) /FL=gb:U33632.1	
(amino acid)	gb:U90065.1 gb:U76996.1 gb:NM_002245.1	
prostaglandin-	gb:NM_000963.1 /DEF=Homo sapiens	204748_at
endoperoxide	prostaglandin-endoperoxide synthase 2	
synthase 2	(prostaglandin GH synthase and	
(prostaglandin G/H	cyclooxygenase) (PTGS2), mRNA.	
synthase and	/FEA=mRNA /GEN=PTGS2	
cyclooxygenase)	/PROD=prostaglandin-endoperoxide synthase	
	2(prostaglandin GH synthase and	
SEQ ID NOS: 47	cyclooxygenase) /DB_XREF=gi:4506264	
(DNA) and 162	/UG=Hs.196384 prostaglandin-endoperoxide	
(amino acid)	synthase 2 (prostaglandin GH synthase and	
	cyclooxygenase) /FL=gb:M90100.1	
	gb:L15326.1 gb:NM_000963.1	
protease inhibitor 3,	gb:NM_002638.1 /DEF=Homo sapiens	203691_at
skin-derived	protease inhibitor 3, skin-derived (SKALP)	
(SKALP)	(PI3), mRNA. /FEA=mRNA /GEN=PI3	
	/PROD=protease inhibitor 3, skin-derived	
SEQ ID NOS: 48	(SKALP) /DB XREF=gi:4505786	
(DNA) and 163	/UG=Hs.112341 protease inhibitor 3, skin-	
(amino acid)	derived (SKALP) /FL=gb:NM 002638.1	
PTPRF interacting	Consensus includes gb:AI692180 /FEA=EST	212841_s_at
protein, binding	/DB_XREF=gi:4969520	
protein 2 (liprin beta	/DB_XREF=est:wd37f06.x1	
2)	/CLONE=IMAGE:2330339 /UG=Hs.12953	
	PTPRF interacting protein, binding protein 2	
SEQ ID NO: 49	(liprin beta 2)	
(DNA)		
retinoic acid receptor	Consensus includes gb:AI669229 /FEA=EST	221872 at
responder (tazarotene	/DB XREF=gi:4834003	
induced) 1	/DB XREF=est:wc13e06.x1	
	1.22_11.21 000.11012000.21	<u> </u>

	/CLONE=IMAGE:2315074 /UG=Hs.82547	
SEQ ID NO: 50	retinoic acid receptor responder (tazarotene	
`	induced) 1	
(DNA)	gb:NM_015366.1 /DEF=Homo sapiens Rho	205980 s at
Rho GTPase		203980_8_ai
activating protein 8	GTPase activating protein 8 (ARHGAP8),	
	mRNA. /FEA=mRNA /GEN=ARHGAP8	
SEQ ID NOS: 51	/PROD=Rho GTPase activating protein 8	
(DNA) and 164	/DB_XREF=gi:7656903 /UG=Hs.102336	
(amino acid)	Rho GTPase activating protein 8	
	/FL=gb:NM_015366.1	
ribonuclease, RNase	gb:NM_002933.1 /DEF=Homo sapiens	201785_at
A family, 1	ribonuclease, RNase A family, 1 (pancreatic)	
(pancreatic)	(RNASE1), mRNA. /FEA=mRNA	
	/GEN=RNASE1 /PROD=ribonuclease,	
SEQ ID NOS: 52	RNase A family, 1 (pancreatic)	
(DNA) and 165	/DB_XREF=gi:4506546 /UG=Hs.78224	•
(amino acid)	ribonuclease, RNase A family, 1 (pancreatic)	
	/FL=gb:BC005324.1 gb:NM_002933.1	
	gb:D26129.1	
serine (or cysteine)	gb:NM 002639.1 /DEF=Homo sapiens serine	204855 at
proteinase inhibitor,	(or cysteine) proteinase inhibitor, clade B	_
clade B (ovalbumin),	(ovalbumin), member 5 (SERPINB5),	
member 5	mRNA. /FEA=mRNA /GEN=SERPINB5	
member 3	/PROD=serine (or cysteine) proteinase	
SEQ ID NOS: 53	inhibitor, cladeB (ovalbumin), member 5	
(DNA) and 166	/DB XREF=gi:4505788 /UG=Hs.55279	
(amino acid)	serine (or cysteine) proteinase inhibitor, clade	
(ammo acid)	B (ovalbumin), member 5	
	/FL=gb:NM_002639.1 gb:U04313.1	
	Consensus includes gb:AI885290 /FEA=EST	213994 s at
spondin 1, (f-spondin)	/DB XREF=gi:5590454	213774_3_at
extracellular matrix		
protein	/DB_XREF=est:wl92a04.x1	
GTG TD 310 54	/CLONE=IMAGE:2432334 /UG=Hs.5378	
SEQ ID NO: 54	spondin 1, (f-spondin) extracellular matrix	
(DNA)	protein TREE II	205226
superoxide dismutase	gb:NM_003102.1 /DEF=Homo sapiens	205236_x_at
3, extracellular	superoxide dismutase 3, extracellular (SOD3),	
	mRNA. /FEA=mRNA /GEN=SOD3	
SEQ ID NOS: 55	/PROD=superoxide dismutase 3, extracellular	
(DNA) and 167	/DB_XREF=gi:4507150 /UG=Hs.2420	
(amino acid)	superoxide dismutase 3, extracellular	
	/FL=gb:J02947.1 gb:NM_003102.1	
tumor necrosis factor	gb:BC002794.1 /DEF=Homo sapiens, tumor	209354_at
receptor superfamily,	necrosis factor receptor superfamily, member	
member 14	14 (herpesvirus entry mediator), clone	
(herpesvirus entry	MGC:3753, mRNA, complete cds.	
mediator)	/FEA=mRNA /PROD=tumor necrosis factor	
,	receptor superfamily, member 14 (herpesvirus	
L		

SEQ ID NOS: 56	entry mediator) /DB_XREF=gi:12803894	
(DNA) and 168	/UG=Hs.279899 tumor necrosis factor	
(amino acid)	receptor superfamily, member 14 (herpesvirus	
	entry mediator) /FL=gb:BC002794.1	
	gb:U70321.1 gb:U81232.1 gb:NM_003820.1	
	gb:AF153978.1	
tumor necrosis factor	gb:NM_000043.1 /DEF=Homo sapiens tumor	204781_s_at
receptor superfamily,	necrosis factor receptor superfamily, member	
member 6	6 (TNFRSF6), mRNA. /FEA=mRNA	
	/GEN=TNFRSF6 /PROD=apoptosis (APO-1)	
SEQ ID NOS: 57	antigen 1 /DB_XREF=gi:4507582	
(DNA) and 169	/UG=Hs.82359 tumor necrosis factor receptor	
(amino acid)	superfamily, member 6 /FL=gb:M67454.1	
	gb:NM_000043.1	
zinc finger protein	gb:NM_003438.1 /DEF=Homo sapiens zinc	207394_at
137 (clone pHZ-30)	finger protein 137 (clone pHZ-30) (ZNF137),	
	mRNA. /FEA=mRNA /GEN=ZNF137	
SEQ ID NOS: 58	/PROD=zinc finger protein 137 (clone pHZ-	
(DNA) and 170	30) /DB_XREF=gi:4507988 /UG=Hs.151689	
(amino acid)	zinc finger protein 137 (clone pHZ-30)	
	/FL=gb:NM_003438.1 gb:U09414.1	
hypothetical protein	Consensus includes gb:AI339568 /FEA=EST	222727_s_at
FLJ22233	/DB_XREF=gi:4076495	
	/DB_XREF=est:qk67e10.x1	
SEQ ID NO: 59	/CLONE=IMAGE:1874058 /UG=Hs.286194	
(DNA)	hypothetical protein FLJ22233	
	/FL=gb:NM_024959.1	
regenerating gene	gb:AY007243.1 /DEF=Homo sapiens	223447_at
type IV	regenerating gene type IV mRNA, complete	
	cds. /FEA=mRNA /PROD=regenerating gene	
SEQ ID NOS: 60	type IV /DB_XREF=gi:12621025	
(DNA) and 171	/UG=Hs.105484 Homo sapiens regenerating	į
(amino acid)	gene type IV mRNA, complete cds	
	/FL=gb:AY007243.1	
Homo sapiens cDNA:	Consensus includes gb:AK025615.1	225285_at
FLJ21962 fis, clone	/DEF=Homo sapiens cDNA: FLJ21962 fis,	
HEP05564	clone HEP05564. /FEA=mRNA	
	/DB_XREF=gi:10438186 /UG=Hs.7567	
SEQ ID NO: 61	Homo sapiens cDNA: FLJ21962 fis, clone	
(DNA)	HEP05564	
ESTs	Consensus includes gb:N37023 /FEA=EST	225407_at
	/DB_XREF=gi:1158165	
SEQ ID NO: 62	/DB_XREF=est:yy40d03.s1	
(DNA)	/CLONE=IMAGE:273701 /UG=Hs.235883	
	ESTs	
phosphoprotein	Consensus includes gb:AK000680.1	225626_at
associated with	/DEF=Homo sapiens cDNA FLJ20673 fis,	
glycosphingolipid-	clone KAIA4464. /FEA=mRNA	

enriched	/DB XREF=gi:7020924 /UG=Hs.266175	
microdomains	phosphoprotein associated with GEMs	
microdomanis		
SEO ID MOS. 62	/FL=gb:AF240634.1 gb:NM_018440.1	
SEQ ID NOS: 63		
(DNA) and 172		
(amino acid)		
prostate cancer	Consensus includes gb:AA633076 /FEA=EST	226167_at
associated protein 7	/DB_XREF=gi:2556490	
·	/DB XREF=est:nq38a06.s1	
SEQ ID NO: 64	/CLONE=IMAGE:1146130 /UG=Hs.27495	
(DNA)	prostate cancer associated protein 7	
Homo sapiens,	Consensus includes gb:AA524690 /FEA=EST	226168 at
Similar to RIKEN	/DB XREF=gi:2265618	220100_41
cDNA 1110060018	/DB XREF=est:ng38e07.s1	
gene, clone	/CLONE=IMAGE:937092 /UG=Hs.294143	
1 = '		
MGC:17236	ESTs, Weakly similar to predicted using	
IMAGE:3864137,	Genefinder C.elegans	
mRNA, complete cds		
SEQ ID NO: 65		
(DNA)		
hypothetical protein	Consensus includes gb:BF111925 /FEA=EST	226171_at
FLJ20209	/DB_XREF=gi:10941704	
1	/DB_XREF=est:7138g05.x1	
SEQ ID NO: 66	/CLONE=IMAGE:3523784 /UG=Hs.3685	
(DNA)	hypothetical protein FLJ20209	
Homo sapiens mRNA	Consensus includes gb:AA532640 /FEA=EST	226484 at
for KIAA1190	/DB XREF=gi:2276894	
protein, partial cds	/DB XREF=est:nj17c04.s1	
F	/CLONE=IMAGE:986598 /UG=Hs.206259	
SEQ ID NOS: 67	Homo sapiens mRNA for KIAA1190 protein,	
(DNA) and 173	partial cds	
(amino acid)	partial ods	
KIAA1543 protein	Congongua includes she AD040076 1	226404 -+
KIAA1343 protein	Consensus includes gb:AB040976.1	226494_at
SEO ID MOS. CO	/DEF=Homo sapiens mRNA for KIAA1543	
SEQ ID NOS: 68	protein, partial cds. /FEA=mRNA	
(DNA) and 174	/GEN=KIAA1543 /PROD=KIAA1543	
(amino acid)	protein /DB_XREF=gi:7959352	
	/UG=Hs.17686 KIAA1543 protein	
hypothetical protein	Consensus includes gb:AK002203.1	226992_at
MGC20702	/DEF=Homo sapiens cDNA FLJ11341 fis,	
	clone PLACE1010786. /FEA=mRNA	
SEQ ID NO: 69	/DB_XREF=gi:7023932 /UG=Hs.10260	
(DNA)	Homo sapiens cDNA FLJ11341 fis, clone	
	PLACE1010786	
Homo sapiens cDNA	Consensus includes gb:AA129774 /FEA=EST	227019 at
FLJ13137 fis, clone	/DB XREF=gi:1690185	
NT2RP3003150	/DB XREF=est:zl16h09.s1	
11121/1 2002120	ADD_ARCH CSCALIONOS.SI	

	/CLONE=IMAGE:502145 /UG=Hs.288905	
SEQ ID NO: 70	Homo sapiens cDNA FLJ13137 fis, clone	
(DNA)	NT2RP3003150	
hypothetical protein	Consensus includes gb:AW138767	227180_at
FLJ23563	/FEA=EST /DB_XREF=gi:6143085	
	/DB_XREF=est:UI-H-BI1-aep-a-12-0-UI.s1	
SEQ ID NO: 71	/CLONE=IMAGE:2719799 /UG=Hs.274256	
(DNA)	hypothetical protein FLJ23563	
ESTs	Consensus includes gb:AW264333	227320_at
	/FEA=EST /DB_XREF=gi:6641075	
SEQ ID NO: 72	/DB_XREF=est:xq98e01.x1	
(DNA)	/CLONE=IMAGE:2758680 /UG=Hs.21835	
1	ESTs	
ESTs	Consensus includes gb:BF589359 /FEA=EST	227354 at
ŧ	/DB XREF=gi:11681683	_
SEQ ID NO: 73	/DB XREF=est:nab25d01.x1	
(DNA)	/CLONE=IMAGE:3266737 /UG=Hs.13256	
	ESTs	
Homo sapiens,	Consensus includes gb:AW001287	227676 at
Similar to RIKEN	/FEA=EST /DB_XREF=gi:5848203	
cDNA 1810037C20	/DB XREF=est:wu27e06.x1	
gene, clone	/CLONE=IMAGE:2521282 /UG=Hs.61265	
MGC:21481	ESTs, Weakly similar to G786_HUMAN	
IMAGE:3852062,	PROTEIN GS3786 H.sapiens	
mRNA, complete cds	1 ROTEM 053760 H.sapiens	
inicia, complete cus		
SEQ ID NO: 74		
(DNA)		
ESTs, Weakly similar	Consensus includes gb:AA557324 /FEA=EST	227702 at
to JX0331 laurate	/DB XREF=gi:2327801	227702_ut
omega-hydroxylase	/DB XREF=est:nl81a02.s1	
[H.sapiens]	/CLONE=IMAGE:1057034 /UG=Hs.26040	
[II.sapiciis]	ESTs, Weakly similar to fatty acid omega-	
SEQ ID NO: 75	hydroxylase H.sapiens	
(DNA)	hydroxyrase 11.sapiens	
	Consensus includes gb:T86159 /FEA=EST	227724 at
Homo sapiens cDNA:		221124_al
FLJ22063 fis, clone	/DB_XREF=gi:714511	
HEP10326	/DB_XREF=est:yd84h07.s1	
GEO ID NO. 76	/CLONE=IMAGE:114973 /UG=Hs.10450	
SEQ ID NO: 76	Homo sapiens cDNA: FLJ22063 fis, clone	
(DNA)	HEP10326	227725
GalNAc alpha-2, 6-	Consensus includes gb:Y11339.2	227725_at
sialyltransferase I,	/DEF=Homo sapiens mRNA for GalNAc	
long form	alpha-2, 6-sialyltransferase I, long form.	
	/FEA=mRNA /PROD=GalNAc alpha-2,6-	
SEQ ID NOS: 77	sialyltransferase I /DB_XREF=gi:7576275	
(DNA) and 175	/UG=Hs.105352 GalNAc alpha-2, 6-	Ì
(amino acid)	sialyltransferase I, long form	

Trom III	Ta	
ESTs, Weakly similar	Consensus includes gb:AI827789 /FEA=EST	228241_at
to JE0350 Anterior	/DB_XREF=gi:5448449	
gradient-2	/DB_XREF=est:wf33a07.x1	
[H.sapiens]	/CLONE=IMAGE:2357364 /UG=Hs.100686	
	ESTs, Weakly similar to JE0350 Anterior	
SEQ ID NO: 78	gradient-2 H.sapiens	
(DNA)	-	
ESTs	Consensus includes gb:AI700341 /FEA=EST	228653 at
į.	/DB XREF=gi:4988241	_
SEQ ID NO: 79	/DB XREF=est:wd06e10.x1	
(DNA)	/CLONE=IMAGE:2327370 /UG=Hs.110406	
	ESTs	
ESTs	Consensus includes gb:BG494007 /FEA=EST	228716 at
	/DB_XREF=gi:13455521	
SEQ ID NO: 80	/DB XREF=est:602542289F1	
(DNA)	/CLONE=IMAGE:4673182 /UG=Hs.203213	
	ESTs	
anterior gradient 2	Consensus includes gb:AI922323 /FEA=EST	228969 at
(Xenepus laevis)	/DB XREF=gi:5658287	
homolog	/DB XREF=est:wn90h03.x1	
, manual g	/CLONE=IMAGE:2453141 /UG=Hs.293380	
SEQ ID NO: 81	ESTs	
(DNA)		
Homo sapiens cDNA:	Consensus includes gb:AK026984.1	229021 at
FLJ23331 fis, clone	/DEF=Homo sapiens cDNA: FLJ23331 fis,	227021_at
HEP12664	clone HEP12664. /FEA=mRNA	
11131 12004	/DB XREF=gi:10439980 /UG=Hs.50742	
SEQ ID NO: 82	Homo sapiens cDNA: FLJ23331 fis, clone	
(DNA)	HEP12664	
ESTs	Consensus includes gb:AI559300 /FEA=EST	229331 at
Lois	/DB XREF=gi:4509505	229331_ai
SEQ ID NO: 83	/DB_XREF=est:tq43d03.x1	
(DNA)	/CLONE=IMAGE:2211557 /UG=Hs.294140	
(DNA)	ESTs	
hypothetical protein	Consensus includes gb:AI830823 /FEA=EST	220420 a at
nypomencai protein	/DB XREF=gi:5451416	229439_s_at
SEO ID NO. 94		
SEQ ID NO: 84	/DB_XREF=est:wj52b06.x1	
(DNA)	/CLONE=IMAGE:2406419 /UG=Hs.95549	
EGT.	hypothetical protein	000657
ESTs	Consensus includes gb:BF431989 /FEA=EST	229657_at
GEO ID NO 25	/DB_XREF=gi:11444103	
SEQ ID NO: 85	/DB_XREF=est:nab84a05.x1	
(DNA)	/CLONE=IMAGE:3274280 /UG=Hs.203213	
T. C.D.	ESTs	
ESTs	Consensus includes gb:BF589413 /FEA=EST	229893_at
	/DB_XREF=gi:11681737	
SEQ ID NO: 86	/DB_XREF=est:nab26b11.x1	
(DNA)	/CLONE=IMAGE:3267020 /UG=Hs.55501	

	ESTs	
brain-specific protein p25 alpha	Consensus includes gb:BG055052 /FEA=EST /DB_XREF=gi:12512386 /DB_XREF=est:nac94g06.x1	230104_s_at
SEQ ID NO: 87 (DNA)	/CLONE=IMAGE:3441995 /UG=Hs.29353 brain-specific protein p25 alpha	
ESTs, Weakly similar to MMHUE4 erythrocyte	Consensus includes gb:BF110588 /FEA=EST /DB_XREF=gi:10940278 /DB_XREF=est:7n39e12.x1	230645_at
membrane protein 4.1, parent splice form [H.sapiens]	/CLONE=IMAGE:3567071 /UG=Hs.150478 ESTs, Weakly similar to KIAA0987 protein H.sapiens	
SEQ ID NO: 88 (DNA)		
ESTs SEQ ID NO: 89 (DNA)	Consensus includes gb:BF592062 /FEA=EST /DB_XREF=gi:11684386 /DB_XREF=est:7n98h06.x1 /CLONE=IMAGE:3572962 /UG=Hs.233890 ESTs	230760_at
hepatocyte nuclear factor 4, alpha SEQ ID NO: 90	Consensus includes gb:AI032108 /FEA=EST /DB_XREF=gi:3250320 /DB_XREF=est:ow92d11.x1 /CLONE=IMAGE:1654293 /UG=Hs.54424	230914_at
(DNA)	hepatocyte nuclear factor 4, alpha	222244
ESTs SEQ ID NO: 91 (DNA)	Consensus includes gb:AW203959 /FEA=EST /DB_XREF=gi:6503431 /DB_XREF=est:UI-H-BI1-aeu-b-12-0-UI.s1 /CLONE=IMAGE:2720590 /UG=Hs.149532 ESTs	230944_at
ESTs SEQ ID NO: 92 (DNA)	Consensus includes gb:AI139990 /FEA=EST /DB_XREF=gi:3647447 /DB_XREF=est:qa47d03.x1 /CLONE=IMAGE:1689893 /UG=Hs.134586 ESTs	231022_at
ESTs SEQ ID NO: 93	Consensus includes gb:AI806131 /FEA=EST /DB_XREF=gi:5392697 /DB_XREF=est:wf06c06.x1	231148_at
(DNA)	/CLONE=IMAGE:2349802 /UG=Hs.99376 ESTs	
hypothetical protein FLJ23045 SEQ ID NO: 94 (DNA)	Consensus includes gb:AB046810.1 /DEF=Homo sapiens mRNA for KIAA1590 protein, partial cds. /FEA=mRNA /GEN=KIAA1590 /PROD=KIAA1590 protein /DB_XREF=gi:10047254 /UG=Hs.101774 hypothetical protein FLJ23045	232083_at
Homo sapiens cDNA:	Consensus includes gb:AK026404.1	232321_at

FLJ22751 fis, clone	/DEF=Homo sapiens cDNA: FLJ22751 fis,	
KAIA0483, highly	clone KAIA0483, highly similar to AF016692	
similar to AF016692	Homo sapiens small intestinal mucin (MUC3)	
Homo sapiens small	mRNA. /FEA=mRNA	
intestinal mucin	/DB XREF=gi:10439257 /UG=Hs.271819	
(MUC3) mRNA	Homo sapiens cDNA: FLJ22751 fis, clone	
(MOCS) IIICVA	KAIA0483, highly similar to AF016692	
SEQ ID NO: 95	Homo sapiens small intestinal mucin (MUC3)	
(DNA)	mRNA	
Homo sapiens PAC		222641 ot
clone RP5-855D21	Consensus includes gb:AC004908	232641_at
Cione RP3-833D21	/DEF=Homo sapiens PAC clone RP5-	.,
SEO ID NOS, 06	855D21 /FEA=CDS_3	
SEQ ID NOS: 96	/DB_XREF=gi:4156179 /UG=Hs.249181	
(DNA), 176 (amino	Homo sapiens PAC clone RP5-855D21	
acid), 177 (amino	·	
acid), and 178 (amino		
acid)		224662
putative microtubule-	Consensus includes gb:AJ251708.1	234669_x_at
binding protein	/DEF=Homo sapiens partial mRNA for	
	putative microtubule-binding protein.	
SEQ ID NO: 97	/FEA=mRNA /PROD=putative microtubule-	
(DNA)	binding protein /DB_XREF=gi:6491740	
	/UG=Hs.326544 putative microtubule-binding	
	protein	
ESTs	Consensus includes gb:AI741469 /FEA=EST	234970_at
	/DB_XREF=gi:5109757	
SEQ ID NO: 98	/DB_XREF=est:wg11b01.x1	
(DNA)	/CLONE=IMAGE:2364745 /UG=Hs.57787	
	ESTs	
ESTs	Consensus includes gb:AI417897 /FEA=EST	235444_at
	/DB_XREF=gi:4261401	
SEQ ID NO: 99	/DB_XREF=est:tg55b06.x1	
(DNA)	/CLONE=IMAGE:2112659 /UG=Hs.235860	
	ESTs	
ESTs	Consensus includes gb:AA827649 /FEA=EST	235515 at
	/DB XREF=gi:2900090	_
SEQ ID NO: 100	/DB XREF=est:od01a12.s1	,
(DNA)	/CLONE=IMAGE:1357918 /UG=Hs.105317	
	ESTs	
ESTs	Consensus includes gb:AI493909 /FEA=EST	235562 at
	/DB XREF=gi:4394912	
SEQ ID NO: 101	/DB XREF=est:qz94e02.x1	
(DNA)	/CLONE=IMAGE:2042234 /UG=Hs.6131	
()	ESTs	
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SEQ ID NO: 102	/DB_XREF=est:AV741130	
(DNA)	/CLONE=CBCATB06/UG=Hs.173704	
	/CDOME CDCWID00/00-119:1/3/04	

	The state of the s	
	ESTs, Moderately similar to ALU8_HUMAN	
	ALU SUBFAMILY SX SEQUENCE	
	CONTAMINATION WARNING ENTRY	
	H.sapiens	
ESTs, Weakly similar	Consensus includes gb:AI864053 /FEA=EST	235678 at
to I38588 reverse	/DB XREF=gi:5528160	_
transcriptase homolog	/DB XREF=est:wj55h10.x1	
	/CLONE=IMAGE:2406787 /UG=Hs.39972	
[H.sapiens]		
and 102	ESTs, Weakly similar to I38588 reverse	
SEQ ID NO: 103	transcriptase homolog H.sapiens	
(DNA)		225056
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SEQ ID NO: 104	/DB_XREF=est:xz91h08.x1	
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	ESTs	
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	/DB XREF=gi:3405370	_
SEQ ID NO: 105	/DB XREF=est:oz01g07.x1	
(DNA)	/CLONE=IMAGE:1674108 /UG=Hs.131933	
(DNA)	ESTs	
TO COM		236548 at
ESTs	Consensus includes gb:AL044570 /FEA=EST	230348_at
	/DB_XREF=gi:5432785	
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(DNA)	/CLONE=DKFZp434L082 /UG=Hs.147975	
	ESTs	
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	/DB XREF=gi:5764915	
SEQ ID NO: 107	/DB XREF=est:wu13a12.x1	
(DNA)	/CLONE=IMAGE:2516830 /UG=Hs.131360	
	ESTs	
ESTs	Consensus includes gb:AI733801 /FEA=EST	237923 at
	/DB XREF=gi:5054914	
SEQ ID NO: 108	_ _	
	/DB_XREF=est:qk39c04.x5 /CLONE=IMAGE:1871334 /UG=Hs.146186	
(DNA)	1	
TO COMP	ESTs	229102 at
ESTs	Consensus includes gb:BF594323 /FEA=EST	238103_at .
	/DB_XREF=gi:11686647	
SEQ ID NO: 109	/DB_XREF=est:7h79g07.x1	
(DNA)	/CLONE=IMAGE:3322236 /UG=Hs.158989	
	ESTs	
Homo sapiens, clone	Consensus includes gb:T69015 /FEA=EST	238422_at
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IMAGE:3940360,	/DB XREF=est:yc31f04.s1	
mRNA, complete cds	/CLONE=IMAGE:82303 /UG=Hs.192728	
initiality, complete out	ESTs	
SEQ ID NO: 110	25.10	
_		
(DNA)	<u></u>	<u> </u>

POT.	0	T 22 20 2 5
ESTs	Consensus includes gb:AA502384 /FEA=EST /DB_XREF=gi:2237351	238956_at
SEQ ID NO: 111	/DB_XREF=est:ne27f11.s1	
(DNA)	/CLONE=IMAGE:898605 /UG=Hs.151529	
	ESTs	İ
ESTs	Consensus includes gb:AI739241 /FEA=EST	238984 at
	/DB_XREF=gi:5101222	
SEQ ID NO: 112	/DB XREF=est:wi14h02.x1	
(DNA)	/CLONE=IMAGE:2390259 /UG=Hs.171480	i.
	ESTs	
ESTs	Consensus includes gb:AA088446 /FEA=EST	239065 at
	/DB_XREF=gi:1633958	
SEQ ID NO: 113	/DB_XREF=est:zl89f04.s1	
(DNA)	/CLONE=IMAGE:511807 /UG=Hs.170298	
	ESTs	
ESTs	Consensus includes gb:AI493046 /FEA=EST	239148_at
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SEQ ID NO: 114	/DB_XREF=est:qz49b04.x1	
(DNA)	/CLONE=IMAGE:2030191 /UG=Hs.146133	
	ESTs	
ESTs	Consensus includes gb:AI243098 /FEA=EST	239966_at
	/DB_XREF=gi:3838495	
SEQ ID NO: 115	/DB_XREF=est:qh26e03.x1	
(DNA)	/CLONE=IMAGE:1845820 /UG=Hs.178398	
	ESTs	
ESTs, Weakly similar	Consensus includes gb:AI633523 /FEA=EST	240106_at
to A49175 Motch B	/DB_XREF=gi:4684853	
protein - mouse	/DB_XREF=est:th68b11.x1	
[M.musculus]	/CLONE=IMAGE:2123805 /UG=Hs.44705	
SEO ID NO. 116	ESTs	
SEQ ID NO: 116		
(DNA)	Conservation lands at A 1200104 (FDA FGF	240020
ESTs	Consensus includes gb:AI300126 /FEA=EST	240830_at
SEC ID NO. 117	/DB_XREF=gi:3959472	,
SEQ ID NO: 117	/DB_XREF=est:qn54f02.x1	
(DNA)	/CLONE=IMAGE:1902075 /UG=Hs.257858 ESTs	
ESTs	 	240064
EO18	Consensus includes gb:AI917390 /FEA=EST	240964_at
SEO ID NO. 110	/DB_XREF=gi:5637245	
SEQ ID NO: 118 (DNA)	/DB_XREF=est:ts79a05.x1 /CLONE=IMAGE:2237456 /UG=Hs.99415	ii.
(דאאל)	/CLONE=IMAGE:223/456/UG=Hs.99415 ESTs	
betacellulin		241412 -4
DETACEHUHHI	Consensus includes gb:AI620677 /FEA=EST	241412_at
SEQ ID NO: 119	/DB_XREF=gi:4629803	
(DNA)	/DB_XREF=est:tu85e09.x1 /CLONE=IMAGE:2257864 /UG=Hs.154191	
(DIVA)	CLONE-IMAGE:223/864/UG=Hs.154191 ESTs	
ESTs		241974 -+
TO 18	Consensus includes gb:H05025 /FEA=EST	241874_at

SEQ ID NO: 120 (DNA)	/DB_XREF=gi:868577 /DB_XREF=est:yl74g12.s1 /CLONE=IMAGE:43864 /UG=Hs.323767	
ESTs	ESTs Consensus includes gb:AW024656	242258
LOIS	/FEA=EST /DB_XREF=gi:5878186	242358_at
SEQ ID NO: 121	/DB XREF=est:wu78h05.x1	
(DNA)	/CLONE=IMAGE:2526201 /UG=Hs.233382	
	ESTs, Moderately similar to AF119917 62	i
DOT	PRO2822 H.sapiens	
ESTs	Consensus includes gb:BF696216 /FEA=EST /DB XREF=gi:11981624	242626_at
SEQ ID NO: 122	/DB_XREF=gr.11981024 /DB_XREF=est:602124536F1	
(DNA)	/CLONE=IMAGE:4281632 /UG=Hs.188724	
	ESTs	
ESTs	Consensus includes gb:N57929 /FEA=EST	242978_x_at
CT 0 TO 110	/DB_XREF=gi:1201819	_
SEQ ID NO: 123	/DB_XREF=est:yv61e06.s1	
(DNA)	/CLONE=IMAGE:247234 /UG=Hs.48100 ESTs	
ESTs, Weakly similar	Consensus includes gb:AI457984 /FEA=EST	242720
to ALU1 HUMAN	/DB_XREF=gi:4312002	243729_at
ALU SUBFAMILY J	/DB_XREF=est:tj66a04.x1	
SEQUENCE	/CLONE=IMAGE:2146446 /UG=Hs.165900	
CONTAMINATION	ESTs, Weakly similar to ALUC_HUMAN	
WARNING ENTRY	!!!! ALU CLASS C WARNING ENTRY !!!	
[H.sapiens]	H.sapiens	
SEQ ID NO: 124		
(DNA)		
ESTs	Consensus includes gb:AA581439 /FEA=EST	244650 at
	/DB_XREF=gi:2359211	
SEQ ID NO: 125	/DB_XREF=est:nh13c10.s1	
(DNA)	/CLONE=IMAGE:952242 /UG=Hs.152328	
	ESTs	

Biological Validation of Biomarker Candidates: Modulation of Expression by Treatment with Ligands for EGFR or by Treatment with Inhibitors for EGFR

To validate the significance of the biomarker candidates to predict the activity of the EGFR pathway and thereby the sensitivity of cancer cell to inhibition of EGFR by therapy, genes that would be regulated by the EGFR pathway were identified. Demonstration of that property for the EGFR biomarker candidates described above would add additional credibility as it would link these genes functionally to the EGFR pathway. Colon cancer and a lung cancer cell lines were treated with epidermal

growth factor, in the absence of serum or, in the presence of serum with the EGFR modulator BMS-461453 or the EGFR modulator cetuximab (also known as C225, a chimeric monoclonal EGFR antibody). To identify genes induced by epidermal growth factor, serum starved cells were treated with 20ng/ml EGF for 0.5, 6, and 18 hours. Control cells were treated with media alone. The expression profiling was performed, and data was analyzed using GeneChip® Expression Analysis software MAS 5.0 (Affymetrix, Santa Clara, California).

Genes inhibited by EGFR antagonists were identified by treating cells in the presence of 10% serum with 0.5uM of BMS-461453 or 1ug/ml or 5ug/ml of C225 for 6 and 24 hours. Cells exposed to 0.05% DMSO were used as the experimental control. Expression profiling was performed, and data were analyzed using GeneChip® Expression Analysis software MAS 5.0.

The gene expression of the inhibitor or EGFR treated cell lines was compared pair-wise to the untreated controls. Polynucleotides from the biomarker list, in which expression was increased two fold with EGFR exposure or decreased two fold with EGFR inhibitor treatment compared to the untreated controls, were considered to be modulated by EGFR. These biomarkers are provided in Table 4. Examples of the biomarkers include EphA1, B-cell translocation gene 2, prostaglandin-endoperoxide synthase 2 and serine (or cysteine) proteinase inhibitor (clade B), which are highly expressed in sensitive cells and up regulated by treatment with EGFR. On the other hand, spondin 1, talin 2 and nuclear receptor subfamily 3 are genes whose expression levels correlate with sensitivity or resistance of colon cancer cell lines and are consistently down regulated by treatment with EGFR inhibitors BMS-461453 and C225. It appears that these biomarkers are likely to be directly or indirectly involved in the EGFR signaling pathway, based on their expression modulation by EGF or EGFR inhibitor treatment.

Identification of Top Biomarkers

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In an attempt to further prioritize biomarkers for use in predicting response of cancer cells to treatment with one or more EGFR modulators, the following filter criteria were used on the Table 4 biomarkers to identify a total of fourteen biomarkers (Table 5) as the top biomarkers:

(1) results from the highly significant correlation of gene expression with IC₅₀: A p-value < 0.01 in the student TTEST or a Pearson value < -0.6 described above;

- (2) results from the modulation of expression by EGFR ligand and/or EGFR inhibitor treatment described above; and
- (3) biomarkers supported by literature revealing a direct relationship between the EGFR pathway and the biomarkers.

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TABLE 5 - Top Fourteen Biomarkers

Biomarker Name	Literature Support Citation	Induced by EGF/ Inhibited by EGFR antagonist
mucin 2, intestinal/tracheal (MUC2)	J Biol Chem. 2002 Aug 30;277(35):32258-67	Expression inhibited 2 fold by EGFR antagonist in GEO colon cancer cell line
intestinal mucin 3 (MUC3)	No	Expression inhibited 2 fold by EGFR antagonist in GEO colon cancer cell line
Homo sapiens cystic fibrosis transmembrane conductance regulator ATP-binding cassette (sub-family C, member 7) (CFTR)	No	Expression stimulated 2 fold by EGFR in H292 lung cancer cell line
f-spondin (KIAA0762) protein	No	Expression inhibited 2 fold by EGFR antagonist in LOVO colon cancer cell line
3-hydroxy-3- methylglutaryl- Coenzyme A synthase 2	J Invest Dermatol. 2000 Jan;114(1):83-7	Expression stimulated 3 fold by EGFR in H292 lung cancer cell line
serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 5 (SERPINB5	Electrophoresis. 2001 Aug;22(14):3001-8.	Expression stimulated 2 fold by EGFR in H292 lung cancer cell line
BTG family, member 2 (BTG2)	No	Expression stimulated 2 fold by EGFR in H292 lung cancer cell line
talin 2 (TLN2)	No	Expression inhibited 2 fold by EGFR antagonist in GEO colon cancer cell line
arachidonic acid	J Biol Chem. 1994 Aug	no

epoxygenase	26;269(34):21786-92.	
prostaglandin G/H	J Biol Chem. 1994 Aug	Expression stimulated 6 fold by
synthase and	26;269(34):21786-92.	EGFR in H292 lung cancer cell line
cyclooxygenase		
EphA1 (EPHA1)	No	Expression stimulated 2 fold by
	· ·	EGFR in CACO2 colon cancer cell
		line
hemoglobin, alpha 1	No	Expression inhibited 2 fold by EGFR
(HBA1)		antagonist in GEO colon cancer cell
		line
bone morphogenetic	Development 2000	no
protein 2	Nov;127(22):4993-5005	
betacellulin (BTC)*	Biochem Biophys Res	no
	Commun. 2002 Jun	
	28;294(5):1040-6	

^{*}The gene betacellulin showed counter regulation with EGFR expression as defined for the EGFR-A list but had just a p value of 0.04 in the Student's TTest for correlation with IC₅₀. It was still selected as a top biomarker for the strong literature support, as betacellulin is one of the published ligands of EGFR.

Utility of Biomarkers

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Polynucleotides that correlate to a specific property of a biological system can be used to make predictions about that biological system and other biological systems. To show the predictive utility of biomarkers that correlate to EGFR modulator sensitivity and resistance, these polynucleotides were tested for their ability to predict the response of twenty two colon cancer cell lines to a small molecule EGFR modulator.

The invention includes single biomarkers including, for example, the fourteen top biomarkers which were tested in a voting scheme. For that purpose, the mean expression value was calculated for all fourteen biomarkers. Colon cancer cell lines which showed an expression level above the mean were then voted to be sensitive, and colon cancer cell lines with expression levels below the mean were voted to be resistant. After this procedure, the voting was compared to the actual sensitivity/resistance status according to the definition based on IC₅₀ (see above) and an error rate was calculated. The error rates of the fourteen top biomarkers are shown in Table 6.

TABLE 6 - Error Rates of Fourteen Top Biomarkers

Biomarker Name	Pearsons value	TTEST P value	Prediction error rate
mucin 2,	-0.531	0.0083	20%

intestinal/tracheal			
(MUC2)			
intestinal mucin 3 (MUC3)	-0.639	0.0004	11.72%
Homo sapiens cystic fibrosis transmembrane conductance regulator ATP-binding cassette (sub-family C, member 7) (CFTR)	-0.646	9E-05	5.9%
f-spondin (KIAA0762) protein	-0.622	0.0004	12.8%
3-hydroxy-3- methylglutaryl- Coenzyme A synthase 2	-0.575	0.0029	21.75%
serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 5 (SERPINB5	-0.62	0.0028	21.75%
BTG family, member 2 (BTG2)	-0.544	0.0042	20.5%
talin 2 (TLN2)	-0.874	3E-05	8.8%
EphA1 (EPHA1)	-0.647	0.0021	22%
hemoglobin, alpha 1 (HBA1)	-0.744	8E-05	20%
bone morphogenetic protein 2	-0.555	0.0091	31.8%
betacellulin (BTC)	-0.536	0.047	43.5%

The biomarkers talin, the Cystic fibrosis conductance regulator (CFTR), and mucin 3 were the best single biomarkers with error rates below 12%.

EXAMPLES:

EXAMPLE 1 - METHODS

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IC50 determination--in vitro cytotoxicity assay

A small molecule EGFR inhibitor, erlotinib HCl (BMS-461453), was tested for cytoxicity *in vitro* against a panel of twenty-two human colon cancer cell lines

available from the American Type Culture Collection. Cytotoxicity was assessed in cells by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) assay (T.L. Riss et al., 1992, *Mol. Biol. Cell*, 3 (Suppl.):184a).

To carry out the assays, the colon cells were plated at 4,000 cell/well in 96 well microtiter plates and 24 hours later serial diluted drugs were added. The concentration range for the EGFR inhibitor was from 5 μ g/ml to 0.0016 μ g/ml (roughly 10 μ M to 0.0032 μ M). The cells were incubated at 37 °C for 72 hours at which time the tetrazolium dye MTS (333 μ g/ml final concentration) in combination with the electron coupling agent phenazine methosulfate (25 μ M final concentration) was added. A dehydrogenase enzyme in live cells reduces the MTS to a form that absorbs light at 492 nm that can be quantified spectrophotometrically. The greater the absorbency, the greater the number of live cells. The results were expressed as an IC₅₀, which is the drug concentration required to inhibit cell proliferation (i.e., absorbance at 450 nm) to 50% of that of untreated control cells. The mean IC₅₀ and standard deviation (SD) from multiple tests for each cell line were calculated.

Resistant/sensitive classification

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The cell lines with IC₅₀ below 6 μ M were defined as sensitive to the EGFR inhibitor, whereas those with IC₅₀ above 6 μ M were considered to be resistant. The resistant/sensitive classification are shown above in Table 1, with five cell lines classified as sensitive and seventeen cell lines classified as resistant.

Gene expression profiling

The colon cells were grown using standard cell culture conditions: RPMI 1640 supplemented to contain 10% fetal bovine serum, 100 IU/ml penicillin, 100 mg/ml streptomycin, 2 mM L-glutamine and 10 mM Hepes (all from GibcoBRL, Rockville, Maryland). RNA was isolated from 50-70% confluent cells or drug-treated cells using the RNeasy™ kits commercially available from Qiagen (Valencia, California). Quality of the RNA was checked by measuring the 28s:18s ribosomal RNA ratio using Agilent 2100 bioanalyzer (Agilent, Technologies, Rockville, Maryland). Concentration of total RNA was determined spectrophotometrically. 10

μg of total RNA from each cell line was used to prepare biotinylated probe according to the Affymetrix Genechip® Expression Analysis Technical Manual, 2001. Targets were hybridized to Affymetrix high density oligonucleotide array human HG-U133 set chips (Affymetrix, Santa Clara, California). Arrays were then washed, and stained using the GeneChip Fluidics station according to the manufacture's instructions. The HG-U133 set consisting of two GeneChip® arrays contains nearly 45,000 probe sets representing more than 39,000 transcripts derived from approximately 33,000 well-substantiated human genes.

10 Preprocessing of microarray data for selecting biomarkers

Scanned image files were visually inspected for artifacts and analyzed with GeneChip® Expression Analysis software MAS 5.0 (Affymetrix, Santa Clara, California). The "Detection Call" (see Affymetrix manual) was used to determine whether a transcript was detected within one sample, as well as the "Signal" (see Affymetrix Genechip® Expression Analysis Technical Manual, 2001) which measured the relative abundance of a transcript. The trimmed mean intensity for each chip was scaled to 1,500 (see Affymetrix manual) in order to account for any minor differences in global chip intensity, so that the overall expression level for each cell line is comparable. Affymetrix control sequences were removed prior to analysis.

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Induction Studies of colon and breast cell lines with EGFR inhibitors or EGFR ligand and selection of genes modulated by the inductions

The five colon cell lines and one lung cell line indicated with asterisks in Table 1 were used in the drug induction study. Three of the colon cell lines express EGFR and are sensitive to the EGFR inhibitor BMS-461453. The SW480 cell line, while expressing EGFR, is insensitive to the EGFR inhibitor, and the COLO320_DM does not express EGFR and is EGFR inhibitor resistant. The lung cancer cell line H292 expresses EGFR, but its sensitivity status is unknown. Cells were seeded in a 10 cm² culture plate with the medium described above and cultured for 24 hours.

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For the EGF induction studies, the colon cell line CACO2 and the lung cancer H292 cell line were washed 2X PBS, and the media was changed to RPMI without serum. The next day the cells were treated with 20 ng/ml EGF, and eventually lysed

for RNA isolation 0.5, 6 and 18 hours post treatment. Gene expression was profiled as described below.

EGFR inhibition studies were conducted on the colon cell lines GEO, CCD33-CO, SW480 and COLO320DM. The expression profiling was performed as described above and data was analyzed using GeneChip® Expression Analysis software MAS 5.0. The expression data of EGFR inhibitor treated cell lines were compared pair-wise to that of untreated same cell line. A change was considered significant if a two fold difference in expression was demonstrated between the treated and the untreated control. Analysis was done for all four cell lines to compare the gene expression with or without EGFR inhibitor treatment.

EXAMPLE 2 - RT-PCR EXPRESSION PROFILING

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RNA quantification was performed using the SYBR Green real-time PCR. The SYBR Green real-time PCR assay is one of the most precise methods for assaying the concentration of nucleic acid templates.

RNA can be prepared using standard methods, preferably, employing the RNeasy Kit commercially available from Qiagen (Valencia, California). cDNA template for real-time PCR can be generated using the SuperscriptTM First Strand Synthesis system for RT-PCR. SYBR Green real-time PCR reactions are prepared as follows: the reaction mix contains 20 ng first strand cDNA; 50 nM Forward Primer; 50 nM Reverse Primer; 0.75X SYBR Green I (Sigma); 1X SYBR Green PCR Buffer (50mMTris-HCl pH 8.3, 75 mM KCl); 10% DMSO; 3 mM MgCl₂; 300 µM each dATP, dGTP, dTTP, dCTP; 1 U Platinum® Taq DNA Polymerase High Fidelity (Cat# 11304-029; Life Technologies; Rockville, Maryland). Real-time PCR is performed using an Applied Biosystems 5700 Sequence Detection System.

Conditions are 95 °C for 10 minutes (denaturation and activation of Platinum® Taq DNA Polymerase), 40 cycles of PCR (95 °C for 15 seconds, 60 °C for 1 minute). PCR products are analyzed for uniform melting using an analysis algorithm built into the 5700 Sequence Detection System.

cDNA quantification used in the normalization of template quantity is performed using SYBR Green real-time PCR. Expression of EGFR is normalized to GAPDH expression as described below.

The sequences for the GAPDH oligonucleotides used in the SYBR Green realtime PCR reactions are:

GAPDH-F: 5'-AGCCGAGCCACATCGCT-3' (SEQ ID NO: 191)

GAPDH-R: 5'-GTGACCAGGCGCCCAATAC-3' (SEQ ID NO: 192)

The sequences for the EGFR oligonucleotides used in the SYBR Green realtime PCR reactions are:

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EGFR-F: 5'- GCGTCTCTTGCCGGAATGT-3' (SEQ ID NO: 193)

EGFR-R: 5'- AGCCGAGGCAGGGAATGCGTG-3' (SEQ ID NO: 194)

The Sequence Detection System generates a Ct (threshold cycle) value that is used to calculate a concentration for each input cDNA template. cDNA levels for each gene of interest are normalized to GAPDH cDNA levels to compensate for variations in total cDNA quantity in the input sample. This is done by generating GAPDH Ct values for each cell line. Ct values for the gene of interest and GAPDH are inserted into a modified version of the δδCt equation (Applied Biosystems

15 Prism® 5700 Sequence Detection System User Manual) which is used to calculate a GAPDH normalized relative cDNA level for each specific cDNA. The δδCt equation is: relative quantity of nucleic acid template =2^{δδCt} = 2^(δCta-δCtb), where δCta = Ct target – Ct GAPDH, and δCtb = Ct reference – Ct GAPDH.

EXAMPLE 3 - PRODUCTION OF ANTIBODIES AGAINST THE BIOMARKERS

Antibodies against the biomarkers can be prepared by a variety of methods. For example, cells expressing an biomarker polypeptide can be administered to an animal to induce the production of sera containing polyclonal antibodies directed to the expressed polypeptides. In one aspect, the biomarker protein is prepared and isolated or otherwise purified to render it substantially free of natural contaminants, using techniques commonly practiced in the art. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity for the expressed and isolated polypeptide.

In one aspect, the antibodies of the invention are monoclonal antibodies (or protein binding fragments thereof). Cells expressing the biomarker polypeptide can be cultured in any suitable tissue culture medium, however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented to contain 10% fetal bovine

serum (inactivated at about 56 °C), and supplemented to contain about 10 g/l nonessential amino acids, about 1,00 U/ml penicillin, and about 100 μ g/ml streptomycin.

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The splenocytes of immunized (and boosted) mice can be extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line can be employed in accordance with the invention, however, it is preferable to employ the parent myeloma cell line (SP2/0), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (1981, *Gastroenterology*, 80:225-232). The hybridoma cells obtained through such a selection are then assayed to identify those cell clones that secrete antibodies capable of binding to the polypeptide immunogen, or a portion thereof.

Alternatively, additional antibodies capable of binding to the biomarker polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens and, therefore, it is possible to obtain an antibody that binds to a second antibody. In accordance with this method, protein specific antibodies can be used to immunize an animal, preferably a mouse. The splenocytes of such an immunized animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones that produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce the formation of further protein-specific antibodies.

25 EXAMPLE 4 - IMMUNOFLUORESCENCE ASSAYS

The following immunofluorescence protocol may be used, for example, to verify EGFR biomarker protein expression on cells or, for example, to check for the presence of one or more antibodies that bind EGFR biomarkers expressed on the surface of cells. Briefly, Lab-Tek II chamber slides are coated overnight at 4 °C with 10 micrograms/milliliter (µg/ml) of boyine collagen Type II in DPBS containing calcium and magnesium (DPBS++). The slides are then washed twice with cold DPBS++ and seeded with 8000 CHO-CCR5 or CHO pC4 transfected cells in a total

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volume of 125 μl and incubated at 37 °C in the presence of 95% oxygen / 5% carbon dioxide.

The culture medium is gently removed by aspiration and the adherent cells are washed twice with DPBS++ at ambient temperature. The slides are blocked with DPBS++ containing 0.2% BSA (blocker) at 0-4 °C for one hour. The blocking solution is gently removed by aspiration, and 125 μl of antibody containing solution (an antibody containing solution may be, for example, a hybridoma culture supernatant which is usually used undiluted, or serum/plasma which is usually diluted, e.g., a dilution of about 1/100 dilution). The slides are incubated for 1 hour at 0-4 °C. Antibody solutions are then gently removed by aspiration and the cells are washed five times with 400 μl of ice cold blocking solution. Next, 125 μl of 1 μg/ml rhodamine labeled secondary antibody (e.g., anti-human IgG) in blocker solution is added to the cells. Again, cells are incubated for 1 hour at 0-4 °C.

The secondary antibody solution is then gently removed by aspiration and the cells are washed three times with 400 μ l of ice cold blocking solution, and five times with cold DPBS++. The cells are then fixed with 125 μ l of 3.7% formaldehyde in DPBS++ for 15 minutes at ambient temperature. Thereafter, the cells are washed five times with 400 μ l of DPBS++ at ambient temperature. Finally, the cells are mounted in 50% aqueous glycerol and viewed in a fluorescence microscope using rhodamine filters.

CLAIMS:

What is claimed is:

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1. A method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises:

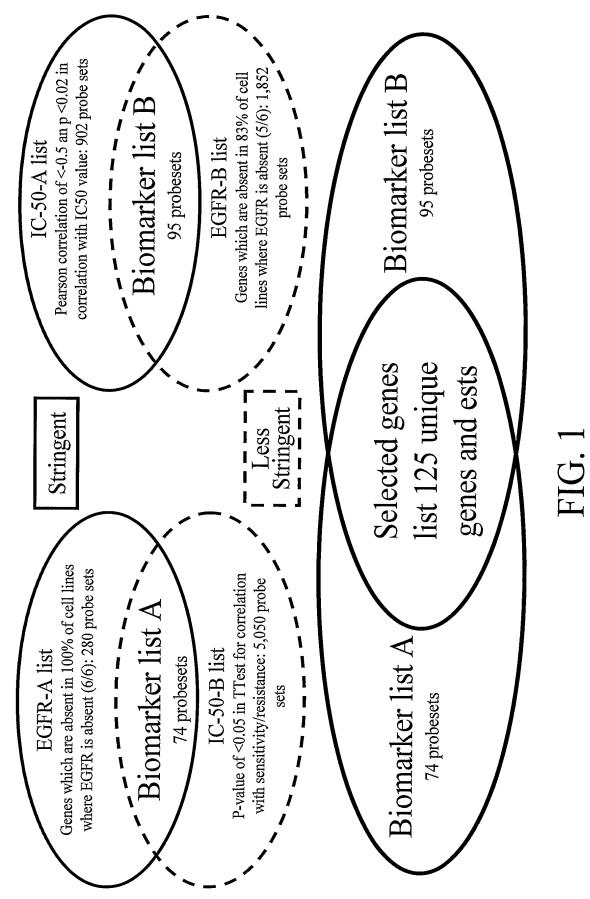
- (a) measuring in the mammal the level of at least one biomarker selected from the biomarkers of Table 4;
 - (b) exposing the mammal to the EGFR modulator;
- (c) following the exposing of step (b), measuring in the mammal the level of the at least one biomarker,

wherein a difference in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates that the mammal will respond therapeutically to said method of treating cancer.

- 2. The method of claim 1 wherein the at least one biomarker is selected from the biomarkers of Table 5.
 - 3. The method of claim 1 wherein the method is an in vitro method, and wherein the at least one biomarker is measured in at least one mammalian biological sample from the mammal.
- 4. A method for identifying a mammal that will respond therapeutically to a
 method of treating cancer comprising administering an EGFR modulator, wherein the method comprises:
 - (a) exposing the mammal to the EGFR modulator;
 - (b) following the exposing of step (a), measuring in the mammal the level of the at least one biomarker selected from the biomarkers of Table 4,

wherein a difference in the level of the at least one biomarker measured in step (b), compared to the level of the biomarker in a mammal that has not been exposed to said EGFR modulator, indicates that the mammal will respond therapeutically to said method of treating cancer.

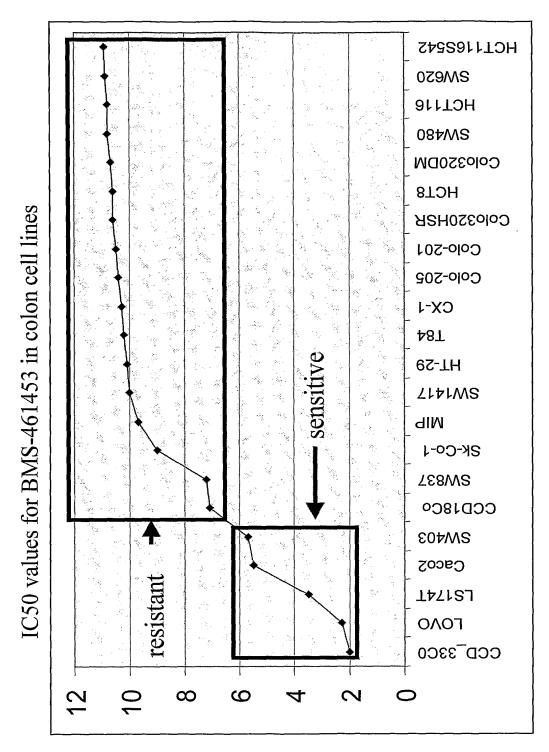
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FIG. 2A



IC50 (Mu)

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185/439

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cagangccaa agcaaagant teetnaaagg tageeggeet gntgecaaac etggggacaa
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Thr Trp Pro Lys Asp Val Gly Ile Leu Ala Leu Glu Val Tyr Phe Pro 50 55

Ala Gln Tyr Val Asp Gln Thr Asp Leu Glu Lys Tyr Asn Asn Val Glu 70 75

Ala Gly Lys Tyr Thr Val Gly Leu Gly Gln Thr Arg Met Gly Phe Cys

Ser Val Gln Glu Asp Ile Asn Ser Leu Cys Leu Thr Val Val Gln Arg

Leu Met Glu Arg Ile Gln Leu Pro Trp Asp Ser Val Gly Arg Leu Glu 120 125

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Pro	Phe 290		Leu	Asp	Asp	Leu 295		Tyr			Phe 300	His	Thr	Pro	Phe
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Leu	. Ser	·Ala	Ser	Ser 325		Thr	Gln	Thr	Ser 330	Leu	ı Tyr	Lys	Gly	Leu 335	Glu
Ala	ı Phe	: Gly	Gly 340		Lys	Leu	Glu	Asp 345		Tyr	Thr	Asn	Lys 350	: Asp	Leu
Asp) Lys	Ala 355		ı Leu	Lys	Ala	Ser 360		. Asp) Met	: Phe	: Asp 365		. Lys	: Thr

Lys Ala Ser Leu Tyr Leu Ser Thr His Asn Gly Asn Met Tyr Thr Ser 370 375 Ser Leu Tyr Gly Cys Leu Ala Ser Leu Leu Ser His His Ser Ala Gln 390 395 Glu Leu Ala Gly Ser Arg Ile Gly Ala Phe Ser Tyr Gly Ser Gly Leu 405 410 Ala Ala Ser Phe Phe Ser Phe Arg Val Ser Gln Asp Ala Ala Pro Gly Ser Pro Leu Asp Lys Leu Val Ser Ser Thr Ser Asp Leu Pro Lys Arg Leu Ala Ser Arg Lys Cys Val Ser Pro Glu Glu Phe Thr Glu Ile Met 450 455 460 Asn Gln Arg Glu Gln Phe Tyr His Lys Val Asn Phe Ser Pro Pro Gly 465 470 Asp Thr Asn Ser Leu Phe Pro Gly Thr Trp Tyr Leu Glu Arg Val Asp 485 490 495 Glu Gln His Arg Arg Lys Tyr Ala Arg Arg Pro Val 500 505 <210> 127 <211> 396 <212> PRT <213> Human <400> 127 Met Val Ala Gly Thr Arg Cys Leu Leu Ala Leu Leu Pro Gln Val 10 Leu Leu Gly Gly Ala Ala Gly Leu Val Pro Glu Leu Gly Arg Arg Lys 20 25 Phe Ala Ala Ala Ser Ser Gly Arg Pro Ser Ser Gln Pro Ser Asp Glu 40 Val Leu Ser Glu Phe Glu Leu Arg Leu Leu Ser Met Phe Gly Leu Lys 50

Gln 65	Arg	Pro	Thr	Pro	Ser 3	Arg :	Asp .	Ala	Val	Val 75	Pro	Pro	Tyr	Met	Leu 80
Asp	Leu	Tyr	Arg	Arg 85	His	Ser	Gly	Gln	Pro 90	Gly	Ser	Pro	Ala	Pro 95	Asp
His	Arg	Leu	Glu 100	Arg	Ala	Ala	Ser	Arg 105	Ala	Asn	Thr	Val	Arg 110	Ser	Phe
His	His	Glu 115	Glu	Ser	Leu	Glu	Glu 120	Leu	Pro	Glu	Thr	Ser 125	Gly	Lys	Thr
Thr	Arg 130	Arg	Phe	Phe	Phe	Asn 135	Leu	Ser	Ser	Ile	Pro 140	Thr	Glu	Glu	Phe
Ile 145	Thr	Ser	Ala	Glu	Leu 150	Gln	Val	Phe	Arg	Glu 155	Gln	Met	Gln	Asp	Ala 160
Leu	Gly	Asn	. Asn	Ser 165	Ser	Phe	His	His	Arg 170	Ile	Asn	Ile	Tyr	Glu 175	Ile
Ile	Lys	Pro	Ala 180		Ala	Asn	Ser	Lys 185	Phe	Pro	Val	Thr	Arg 190	Leu	Leu
Asp	> Thr	195		ı Val	. Asn	Gln	Asn 200	Ala	Ser	Arg	Trp	Glu 205	. Ser	Phe	a Asp
Val	Th:		o Ala	a Val	. Met	Arg 215	Trp	Thr	Ala	Glr.	Gly 220	His	al Al ā	a Asr	n His
Gl <u>s</u> 22		e Vai	l Val	l Glı	ı Val 230	. Ala	. His	. Leu	ı Glu	a Glu 235	ı Lys	s Glr	ı Gl	y Val	L Ser 240
ГÀ	s Ar	g Hi	s Vai	l Arc 24		e Ser	: Arg	g Ser	: Let 250	ı His	s Glr	n Asp	o Gli	Hi: 25.	s Ser 5
Tr	p Se	r Gl	n Il 26		g Pro) Lev	ı Leı	ı Val 265	L Th:	r Pho	e Gl	y His	s As; 27	p Gl; 0	y Lys
Gl	y Hi	s Pr 27		u Hi	s Ly:	a Arç	g Gl: 28	а Ь у:	s Ar	g Gl:	n Ala	a Ly: 28!	s Hi 5	s Ly	s Gln
Ar	g Ly 29	_	g Le	u Ly	s Se:	r Se: 29!	r Cy	s Ly	s Ar	g Hi	s Pr	o Le	u Ty	r Va	l Asp

Phe Ser Asp Val Gly Trp Asn Asp Trp Ile Val Ala Pro Pro Gly Tyr 305 310 315 320

His Ala Phe Tyr Cys His Gly Glu Cys Pro Phe Pro Leu Ala Asp His 325 330 335

Leu Asn Ser Thr Asn His Ala Ile Val Gln Thr Leu Val Asn Ser Val 340 345 350

Asn Ser Lys Ile Pro Lys Ala Cys Cys Val Pro Thr Glu Leu Ser Ala 355 360 365

Ile Ser Met Leu Tyr Leu Asp Glu Asn Glu Lys Val Val Leu Lys Asn 370 375 380

Tyr Gln Asp Met Val Val Glu Gly Cys Gly Cys Arg 385 390 395

<210> 128

<211> 219

<212> PRT

<213> Human

<400> 128

Met Ala Asp Lys Ala Lys Pro Ala Lys Ala Ala Asn Arg Thr Pro Pro 1 5 10 15

Lys Ser Pro Gly Asp Pro Ser Lys Asp Arg Ala Ala Lys Arg Leu Ser 20 25 30

Leu Glu Ser Glu Gly Ala Gly Glu Gly Ala Ala Ser Pro Glu Leu 35 40 45

Ser Ala Leu Glu Glu Ala Phe Arg Arg Phe Ala Val His Gly Asp Ala 50 55 60

Arg Ala Thr Gly Arg Glu Met His Gly Lys Asn Trp Ser Lys Leu Cys 70 75 80

Lys Asp Cys Gln Val Ile Asp Gly Arg Asn Val Thr Val Thr Asp Val 85 90 95

Asp Ile Val Phe Ser Lys Ile Lys Gly Lys Ser Cys Arg Thr Ile Thr 100 105 110

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Phe Glu Gln Phe Gln Glu Ala Leu Glu Glu Leu Ala Lys Lys Arg Phe 115 120 125

Lys Asp Lys Ser Ser Glu Glu Ala Val Arg Glu Val His Arg Leu Ile 130 135 140

Glu Gly Lys Ala Pro Ile Ile Ser Gly Val Thr Lys Ala Ile Ser Ser 145 150 155 160

Pro Thr Val Ser Arg Leu Thr Asp Thr Thr Lys Phe Thr Gly Ser His
165 170 175

Lys Glu Arg Phe Asp Pro Ser Gly Lys Gly Lys Gly Lys Ala Gly Arg 180 185 190

Val Asp Leu Val Asp Glu Ser Gly Tyr Val Ser Gly Tyr Lys His Ala 195 200 205

Gly Thr Tyr Asp Gln Lys Val Gln Gly Gly Lys 210 215

<210> 129

<211> 384

<211> 304 <212> PRT

<213> Human

<400> 129

Met Asp Cys Ser Asn Gly Ser Ala Glu Cys Thr Gly Glu Gly Gly Ser 1 5 10 15

Lys Glu Val Val Gly Thr Phe Lys Ala Lys Asp Leu Ile Val Thr Pro 20 25 30

Ala Thr Ile Leu Lys Glu Lys Pro Asp Pro Asn Asn Leu Val Phe Gly 35 40 45

Thr Val Phe Thr Asp His Met Leu Thr Val Glu Trp Ser Ser Glu Phe 50 55 60

Gly Trp Glu Lys Pro His Ile Lys Pro Leu Gln Asn Leu Ser Leu His 65 70 75 80

Pro Gly Ser Ser Ala Leu His Tyr Ala Val Glu Leu Phe Glu Gly Leu 85 90 95

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Lys Ala Phe Arg Gly Val Asp Asn Lys Ile Arg Leu Phe Gln Pro Asn Leu Asn Met Asp Arg Met Tyr Arg Ser Ala Val Arg Ala Thr Leu Pro Val Phe Asp Lys Glu Glu Leu Leu Glu Cys Ile Gln Gln Leu Val Lys Leu Asp Gln Glu Trp Val Pro Tyr Ser Thr Ser Ala Ser Leu Tyr Ile Arg Pro Ala Phe Ile Gly Thr Glu Pro Ser Leu Gly Val Lys Lys Pro Thr Lys Ala Leu Leu Phe Val Leu Leu Ser Pro Val Gly Pro Tyr Phe 185 , Ser Ser Gly Thr Phe Asn Pro Val Ser Leu Trp Ala Asn Pro Lys Tyr Val Arg Ala Trp Lys Gly Gly Thr Gly Asp Cys Lys Met Gly Gly Asn Tyr Gly Ser Ser Leu Phe Ala Gln Cys Glu Asp Val Asp Asn Gly Cys Gln Gln Val Leu Trp Leu Tyr Gly Arg Asp His Gln Ile Thr Glu Val Gly Thr Met Asn Leu Phe Leu Tyr Trp Ile Asn Glu Asp Gly Glu Glu Glu Leu Ala Thr Pro Pro Leu Asp Gly Ile Ile Leu Pro Gly Val Thr Arg Arg Cys Ile Leu Asp Leu Ala His Gln Trp Gly Glu Phe Lys Val Ser Glu Arg Tyr Leu Thr Met Asp Asp Leu Thr Thr Ala Leu Glu Gly Asn Arg Val Arg Glu Met Phe Ser Ser Gly Thr Ala Cys Val Val Cys

325 330 335

Pro Val Ser Asp Ile Leu Tyr Lys Gly Glu Thr Ile His Ile Pro Thr 340 345 350

Met Glu Asn Gly Pro Lys Leu Ala Ser Arg Ile Leu Ser Lys Leu Thr 355 360 365

Asp Ile Gln Tyr Gly Arg Glu Glu Ser Asp Trp Thr Ile Val Leu Ser 370 375 380

<210> 130

<211> 158

<212> PRT

<213> Human

<400> 130

Met Ser His Gly Lys Gly Thr Asp Met Leu Pro Glu Ile Ala Ala Ala 1 5 10 15

Val Gly Phe Leu Ser Ser Leu Leu Arg Thr Arg Gly Cys Val Ser Glu 20 25 30

Gln Arg Leu Lys Val Phe Ser Gly Ala Leu Gln Glu Ala Leu Thr Glu 35 40 45

His Tyr Lys His His Trp Phe Pro Glu Lys Pro Ser Lys Gly Ser Gly 50 55

Tyr Arg Cys Ile Arg Ile Asn His Lys Met Asp Pro Ile Ile Ser Arg 65 70 75 80

Val Ala Ser Gln Ile Gly Leu Ser Gln Pro Gln Leu His Gln Leu Leu 85 90 95

Pro Ser Glu Leu Thr Leu Trp Val Asp Pro Tyr Glu Val Ser Tyr Arg 100 105 110

Ile Gly Glu Asp Gly Ser Ile Cys Val Leu Tyr Glu Glu Ala Pro Leu 115 120 125

Ala Ala Ser Cys Gly Leu Leu Thr Cys Lys Asn Gln Val Leu Leu Gly 130 135 140

Arg Ser Ser Pro Ser Lys Asn Tyr Val Met Ala Val Ser Ser

145 150 155

<210> 131

<211> 344

<212> PRT

<213> Human

<400> 131

Met Gly Pro Pro Ser Ala Pro Pro Cys Arg Leu His Val Pro Trp Lys 1 5 10 15

Glu Val Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr 20 25 30

Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly 35 40 45

Lys Glu Val Leu Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly 50 55 60

Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val 65 70 75 80

Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser 85 90 95

Gly Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val 100 105 110

Thr Gln Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp 115 120 125

Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu 130 135 140

Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys 145 150 155 160

Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr 165 170 175

Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Arg Leu Gln 180 185 190

Leu Ser Asn Gly Asn Met Thr Leu Thr Leu Leu Ser Val Lys Arg Asn

195 200 205

Asp Ala Gly Ser Tyr Glu Cys Glu Ile Gln Asn Pro Ala Ser Ala Asn 210 215 220

Arg Ser Asp Pro Val Thr Leu Asn Val Leu Tyr Gly Pro Asp Val Pro 225 230 235 240

Thr Ile Ser Pro Ser Lys Ala Asn Tyr Arg Pro Gly Glu Asn Leu Asn 245 250 255

Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Phe 260 265 270

Ile Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn 275 280 285

Ile Thr Val Asn Asn Ser Gly Ser Tyr Met Cys Gln Ala His Asn Ser 290 295 300

Ala Thr Gly Leu Asn Arg Thr Thr Val Thr Met Ile Thr Val Ser Gly 305 310 315 320

Ser Ala Pro Val Leu Ser Ala Val Ala Thr Val Gly Ile Thr Ile Gly 325 330 335

Val Leu Ala Arg Val Ala Leu Ile 340

<210> 132

<211> 479

<212> PRT

<213> Human

<400> 132

Met Lys Ser Gln Gly Gln His Trp Tyr Ser Ser Ser Asp Lys Asn Cys 1 5 10 15

Lys Val Ser Phe Arg Glu Lys Leu Leu Ile Ile Asp Ser Asn Leu Gly 20 25 30

Val Gln Asp Val Glu Asn Leu Lys Phe Leu Cys Ile Gly Leu Val Pro 35 40 45

Asn Lys Lys Leu Glu Lys Ser Ser Ser Ala Ser Asp Val Phe Glu His

50 55 60

Leu Leu Ala Glu Asp Leu Leu Ser Glu Glu Asp Pro Phe Phe Leu Ala 65 70 75 80

Glu Leu Leu Tyr Ile Ile Arg Gln Lys Lys Leu Leu Gln His Leu Asn 85 90 95

Cys Thr Lys Glu Glu Val Glu Arg Leu Leu Pro Thr Arg Gln Arg Val 100 105 110

Ser Leu Phe Arg Asn Leu Leu Tyr Glu Leu Ser Glu Gly Ile Asp Ser 115 120 125

Glu Asn Leu Lys Asp Met Ile Phe Leu Leu Lys Asp Ser Leu Pro Lys 130 135 140

Thr Glu Met Thr Ser Leu Ser Phe Leu Ala Phe Leu Glu Lys Gln Gly 145 150 155 160

Lys Ile Asp Glu Asp Asn Leu Thr Cys Leu Glu Asp Leu Cys Lys Thr 165 170 175

Val Val Pro Lys Leu Leu Arg Asn Ile Glu Lys Tyr Lys Arg Glu Lys 180 185 190

Ala Ile Gl
n Ile Val Thr Pro Pro Val Asp Lys Glu Ala Glu Ser Tyr 195 200 205

Gln Gly Glu Glu Leu Val Ser Gln Thr Asp Val Lys Thr Phe Leu 210 215 220

Glu Ala Leu Pro Arg Ala Ala Val Tyr Arg Met Asn Arg Asn His Arg 225 230 235 240

Gly Leu Cys Val Ile Val Asn Asn His Ser Phe Thr Ser Leu Lys Asp 245 250 255

Arg Gln Gly Thr His Lys Asp Ala Glu Ile Leu Ser His Val Phe Gln 260 265 270

Trp Leu Gly Phe Thr Val His Ile His Asn Asn Val Thr Lys Val Glu 275 280 285

Met Glu Met Val Leu Gln Lys Gln Lys Cys Asn Pro Ala His Ala Asp 295 290 Gly Asp Cys Phe Val Phe Cys Ile Leu Thr His Gly Arg Phe Gly Ala 315 310 Val Tyr Ser Ser Asp Glu Ala Leu Ile Pro Ile Arg Glu Ile Met Ser 325 330 His Phe Thr Ala Leu Gln Cys Pro Arg Leu Ala Glu Lys Pro Lys Leu 345 Phe Phe Ile Gln Ala Cys Gln Gly Glu Glu Ile Gln Pro Ser Val Ser 360 Ile Glu Ala Asp Ala Leu Asn Pro Glu Gln Ala Pro Thr Ser Leu Gln 380 Asp Ser Ile Pro Ala Glu Ala Asp Phe Leu Leu Gly Leu Ala Thr Val 395 385 Pro Gly Tyr Val Ser Phe Arg His Val Glu Glu Gly Ser Trp Tyr Ile Gln Ser Leu Cys Asn His Leu Lys Lys Leu Val Pro Arg His Glu Asp 425 420 Ile Leu Ser Ile Leu Thr Ala Val Asn Asp Asp Val Ser Arg Arg Val 440 435 Asp Lys Gln Gly Thr Lys Lys Gln Met Pro Gln Pro Ala Phe Thr Leu 455 Arg Lys Lys Leu Val Phe Pro Val Pro Leu Asp Ala Leu Ser Ile 470 <210> 133 <211> 509 <212> PRT <213> Human <400> 133 Met Thr Val Glu Gly Arg Leu Leu Val Pro Asp Arg Ile Asn Gly Thr 15 10 5

301/439

Ala Asn Lys Met Asn Gly Ala Leu Asp His Ser Asp Gln Pro Asp Pro 20 25 30

Asp Ala Ile Lys Met Phe Val Gly Gln Ile Pro Arg Ser Trp Ser Glu 35 40 45

Lys Glu Leu Lys Glu Leu Phe Glu Pro Tyr Gly Ala Val Tyr Gln Ile 50 55

Asn Val Leu Arg Asp Arg Ser Gln Asn Pro Pro Gln Ser Lys Gly Cys 65 70 75 80

Cys Phe Val Thr Phe Tyr Thr Arg Lys Ala Ala Leu Glu Ala Gln Asn 85 90 95

Ala Leu His Asn Ile Lys Thr Leu Pro Gly Met His His Pro Ile Gln
100 105 110

Met Lys Pro Ala Asp Ser Glu Lys Ser Asn Ala Val Glu Asp Arg Lys 115 120 125

Leu Phe Ile Gly Met Val Ser Lys Lys Cys Asn Glu Asn Asp Ile Arg 130 135 140

Val Met Phe Ser Pro Phe Gly Gln Ile Glu Glu Cys Arg Ile Leu Arg 145 150 155 160

Gly Pro Asp Gly Leu Ser Arg Gly Cys Ala Phe Val Thr Phe Ser Thr 165 170 175

Arg Ala Met Ala Gln Asn Ala Ile Lys Ala Met His Gln Ser Gln Thr 180 185 190

Met Glu Gly Cys Ser Ser Pro Ile Val Val Lys Phe Ala Asp Thr Gln 195 200 205

Lys Asp Lys Glu Gln Arg Arg Leu Gln Gln Gln Leu Ala Gln Gln Met 210 215 220

Gln Gln Leu Asn Thr Ala Thr Trp Gly Asn Leu Thr Gly Leu Gly Gly 225 230 235 240

Leu Thr Pro Gln Tyr Leu Ala Leu Leu Gln Gln Ala Thr Ser Ser Ser 245

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Asn Leu Gly Ala Phe Ser Gly Ile Gln Gln Met Ala Gly Met Asn Ala 260 265 270

Leu Gln Leu Gln Asn Leu Ala Thr Leu Ala Ala Ala Ala Ala Ala Ala 275 280 285

Gln Thr Ser Ala Thr Ser Thr Asn Ala Asn Pro Leu Ser Thr Thr Ser 290 295 300

Ser Ala Leu Gly Ala Leu Thr Ser Pro Val Ala Ala Ser Thr Pro Asn 305 310 315 320

Ser Thr Ala Gly Ala Ala Met Asn Ser Leu Thr Ser Leu Gly Thr Leu 325 330 335

Gln Gly Leu Ala Gly Ala Thr Val Gly Leu Asn Asn Ile Asn Ala Leu 340 345 350

Ala Val Ala Gln Met Leu Ser Gly Met Ala Ala Leu Asn Gly Gly Leu 355 360 365

Gly Ala Thr Gly Leu Thr Asn Gly Thr Ala Gly Thr Met Asp Ala Leu 370 375 380

Thr Gln Ala Tyr Ser Gly Ile Gln Gln Tyr Ala Ala Ala Ala Leu Pro 385 390 395

Thr Leu Tyr Ser Gln Ser Leu Leu Gln Gln Gln Ser Ala Ala Gly Ser 405 410 415

Gln Lys Glu Gly Pro Glu Gly Ala Asn Leu Phe Ile Tyr His Leu Pro 420 425 430

Gln Glu Phe Gly Asp Gln His Ile Leu Gln Met Phe Met Pro Phe Gly 435 440 445

Asn Val Ile Ser Ala Lys Val Phe Ile Asp Lys Gln Thr Asn Leu Ser 450 460

Lys Cys Phe Gly Phe Val Ser Tyr Asp Asn Pro Val Ser Ala Gln Ala 465 470 475 480

Ala Ile Gln Ala Met Asn Gly Phe Gln Ile Gly Met Lys Arg Leu Lys 485 490 495

Val Gln Leu Lys Arg Ser Lys Asn Asp Ser Lys Pro Tyr 500 505

<210> 134

<211> 141

<212> PRT

<213> Human

<400> 134

Met Ala Arg Pro Leu Cys Thr Leu Leu Leu Leu Met Ala Thr Leu Ala 1 5 10 15

Gly Ala Leu Ala Ser Ser Ser Lys Glu Glu Asn Arg Ile Ile Pro Gly
20 25 30

Gly Ile Tyr Asp Ala Asp Leu Asn Asp Glu Trp Val Gln Arg Ala Leu 35 40 45

His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Glu Asp Glu Tyr Tyr 50 55 60

Arg Arg Pro Leu Gln Val Leu Arg Ala Arg Glu Gln Thr Phe Gly Gly 65 70 75 80

Val Asn Tyr Phe Phe Asp Val Glu Val Gly Arg Thr Ile Cys Thr Lys 85 90 95

Ser Gln Pro Asn Leu Asp Thr Cys Ala Phe His Glu Gln Pro Glu Leu 100 105 110

Gln Lys Lys Gln Leu Cys Ser Phe Glu Ile Tyr Glu Val Pro Trp Glu 115 120 125

Asp Arg Met Ser Leu Val Asn Ser Arg Cys Gln Glu Ala 130 135 140

<210> 135

<211> 1480

<212> PRT

<213> Human

<400> 135

Met Gln Arg Ser Pro Leu Glu Lys Ala Ser Val Val Ser Lys Leu Phe 1 5 10 15

304/439

Phe Ser Trp Thr Arg Pro Ile Leu Arg Lys Gly Tyr Arg Gln Arg Leu 20 25 30

Glu Leu Ser Asp Ile Tyr Gln Ile Pro Ser Val Asp Ser Ala Asp Asn 35 40 45

Leu Ser Glu Lys Leu Glu Arg Glu Trp Asp Arg Glu Leu Ala Ser Lys 50 55 60

Lys Asn Pro Lys Leu Ile Asn Ala Leu Arg Arg Cys Phe Phe Trp Arg 65 70 75 80

Phe Met Phe Tyr Gly Ile Phe Leu Tyr Leu Gly Glu Val Thr Lys Ala 85 90 95

Val Gln Pro Leu Leu Gly Arg Ile Ile Ala Ser Tyr Asp Pro Asp 100 105 110

Asn Lys Glu Glu Arg Ser Ile Ala Ile Tyr Leu Gly Ile Gly Leu Cys 115 120 125

Leu Leu Phe Ile Val Arg Thr Leu Leu Leu His Pro Ala Ile Phe Gly 130 135

Leu His His Ile Gly Met Gln Met Arg Ile Ala Met Phe Ser Leu Ile 145 150 155 160

Tyr Lys Lys Thr Leu Lys Leu Ser Ser Arg Val Leu Asp Lys Ile Ser 165 170 175

Ile Gly Gln Leu Val Ser Leu Leu Ser Asn Asn Leu Asn Lys Phe Asp 180 185 190

Glu Gly Leu Ala Leu Ala His Phe Val Trp Ile Ala Pro Leu Gln Val 195 200 205

Ala Leu Leu Met Gly Leu Ile Trp Glu Leu Leu Gln Ala Ser Ala Phe 210 215 220

Cys Gly Leu Gly Phe Leu Ile Val Leu Ala Leu Phe Gln Ala Gly Leu 225 230 235 240

Gly Arg Met Met Lys Tyr Arg Asp Gln Arg Ala Gly Lys Ile Ser 245 250 255

Glu Arg Leu Val Ile Thr Ser Glu Met Ile Glu Asn Ile Gln Ser Val 260 265 270

Lys Ala Tyr Cys Trp Glu Glu Ala Met Glu Lys Met Ile Glu Asn Leu 275 280 285

Arg Gln Thr Glu Leu Lys Leu Thr Arg Lys Ala Ala Tyr Val Arg Tyr 290 295 300

Phe Asn Ser Ser Ala Phe Phe Phe Ser Gly Phe Phe Val Val Phe Leu 305 310 315 320

Ser Val Leu Pro Tyr Ala Leu Ile Lys Gly Ile Ile Leu Arg Lys Ile 325 330 335

Phe Thr Thr Ile Ser Phe Cys Ile Val Leu Arg Met Ala Val Thr Arg 340 345 350

Gln Phe Pro Trp Ala Val Gln Thr Trp Tyr Asp Ser Leu Gly Ala Ile 355 360 365

Asn Lys Ile Gln Asp Phe Leu Gln Lys Gln Glu Tyr Lys Thr Leu Glu 370 375 380

Tyr Asn Leu Thr Thr Glu Val Val Met Glu Asn Val Thr Ala Phe 385 390 395 400

Trp Glu Glu Gly Phe Gly Glu Leu Phe Glu Lys Ala Lys Gln Asn Asn 405 410 415

Asn Asn Arg Lys Thr Ser Asn Gly Asp Asp Ser Leu Phe Phe Ser Asn 420 425 430

Phe Ser Leu Leu Gly Thr Pro Val Leu Lys Asp Ile Asn Phe Lys Ile 435 440 445

Glu Arg Gly Gln Leu Leu Ala Val Ala Gly Ser Thr Gly Ala Gly Lys 450 455 460

Thr Ser Leu Leu Met Met Ile Met Gly Glu Leu Glu Pro Ser Glu Gly 465 470 475 480

Lys Ile Lys His Ser Gly Arg Ile Ser Phe Cys Ser Gln Phe Ser Trp

306/439

485 490 495

Ile Met Pro Gly Thr Ile Lys Glu Asn Ile Ile Phe Gly Val Ser Tyr 500 505 510

Asp Glu Tyr Arg Tyr Arg Ser Val Ile Lys Ala Cys Gln Leu Glu Glu 515 520 525

Asp Ile Ser Lys Phe Ala Glu Lys Asp Asn Ile Val Leu Gly Glu Gly 530 535 540

Gly Ile Thr Leu Ser Gly Gly Gln Arg Ala Arg Ile Ser Leu Ala Arg 545 550 555 560

Ala Val Tyr Lys Asp Ala Asp Leu Tyr Leu Leu Asp Ser Pro Phe Gly 565 570 575

Tyr Leu Asp Val Leu Thr Glu Lys Glu Ile Phe Glu Ser Cys Val Cys 580 585 590

Lys Leu Met Ala Asn Lys Thr Arg Ile Leu Val Thr Ser Lys Met Glu 595 600 605

His Leu Lys Lys Ala Asp Lys Ile Leu Ile Leu Asn Glu Gly Ser Ser 610 620

Tyr Phe Tyr Gly Thr Phe Ser Glu Leu Gln Asn Leu Gln Pro Asp Phe 625 630 635 640

Ser Ser Lys Leu Met Gly Cys Asp Ser Phe Asp Gln Phe Ser Ala Glu 645 650 655

Arg Arg Asn Ser Ile Leu Thr Glu Thr Leu His Arg Phe Ser Leu Glu 660 665 670

Gly Asp Ala Pro Val Ser Trp Thr Glu Thr Lys Lys Gln Ser Phe Lys 675 680 685

Gln Thr Gly Glu Phe Gly Glu Lys Arg Lys Asn Ser Ile Leu Asn Pro 690 695 700

Ile Asn Ser Ile Arg Lys Phe Ser Ile Val Gln Lys Thr Pro Leu Gln 705 710 715 720

Met Asn Gly Ile Glu Glu Asp Ser Asp Glu Pro Leu Glu Arg Arg Leu Ser Leu Val Pro Asp Ser Glu Gln Gly Glu Ala Ile Leu Pro Arg Ile Ser Val Ile Ser Thr Gly Pro Thr Leu Gln Ala Arg Arg Gln Ser Val Leu Asn Leu Met Thr His Ser Val Asn Gln Gly Gln Asn Ile His Arg Lys Thr Thr Ala Ser Thr Arg Lys Val Ser Leu Ala Pro Gln Ala Asn Leu Thr Glu Leu Asp Ile Tyr Ser Arg Arg Leu Ser Gln Glu Thr Gly Leu Glu Ile Ser Glu Glu Ile Asn Glu Glu Asp Leu Lys Glu Cys Leu Phe Asp Asp Met Glu Ser Ile Pro Ala Val Thr Thr Trp Asn Thr Tyr Leu Arg Tyr Ile Thr Val His Lys Ser Leu Ile Phe Val Leu Ile Trp Cys Leu Val Ile Phe Leu Ala Glu Val Ala Ala Ser Leu Val Val Leu Trp Leu Leu Gly Asn Thr Pro Leu Gln Asp Lys Gly Asn Ser Thr His Ser Arg Asn Asn Ser Tyr Ala Val Ile Ile Thr Ser Thr Ser Ser Tyr Tyr Val Phe Tyr Ile Tyr Val Gly Val Ala Asp Thr Leu Leu Ala Met Gly Phe Phe Arg Gly Leu Pro Leu Val His Thr Leu Ile Thr Val Ser Lys Ile Leu His His Lys Met Leu His Ser Val Leu Gln Ala Pro

Met Ser Thr Leu Asn Thr Leu Lys Ala Gly Gly Ile Leu Asn Arg Phe 965 970 975

- Ser Lys Asp Ile Ala Ile Leu Asp Asp Leu Leu Pro Leu Thr Ile Phe 980 985 990
- Asp Phe Ile Gln Leu Leu Ile Val Ile Gly Ala Ile Ala Val Val 995 1000 1005
- Ala Val Leu Gln Pro Tyr Ile Phe Val Ala Thr Val Pro Val Ile 1010 1015 1020
- Val Ala Phe Ile Met Leu Arg Ala Tyr Phe Leu Gln Thr Ser Gln 1025 1030 1035
- Gln Leu Lys Gln Leu Glu Ser Glu Gly Arg Ser Pro Ile Phe Thr 1040 1045 1050
- His Leu Val Thr Ser Leu Lys Gly Leu Trp Thr Leu Arg Ala Phe 1055 1060 1065
- Gly Arg Gln Pro Tyr Phe Glu Thr Leu Phe His Lys Ala Leu Asn 1070 1075 1080
- Leu His Thr Ala Asn Trp Phe Leu Tyr Leu Ser Thr Leu Arg Trp 1085 1090 1095
- Phe Gln Met Arg Ile Glu Met Ile Phe Val Ile Phe Phe Ile Ala 1100 1105 1110
- Val Thr Phe Ile Ser Ile Leu Thr Thr Gly Glu Gly Glu Gly Arg 1115 1120 1125
- Val Gly Ile Ile Leu Thr Leu Ala Met Asn Ile Met Ser Thr Leu 1130 1135 1140
- Gln Trp Ala Val Asn Ser Ser Ile Asp Val Asp Ser Leu Met Arg 1145 1150 1155
- Ser Val Ser Arg Val Phe Lys Phe Ile Asp Met Pro Thr Glu Gly 1160 1165 1170
- Lys Pro Thr Lys Ser Thr Lys Pro Tyr Lys Asn Gly Gln Leu Ser 1175 1180 1185

Lys	Val 1190		Ile	Ile	Glu	Asn 1195	Ser	His	Val	Lys	Lys 1200	Asp	Asp	Ile
Trp	Pro 1205	Ser	Gly	Gly	Gln	Met 1210	Thr	Val	Lys	Asp	Leu 1215	Thr	Ala	Lys
Tyr	Thr 1220		Gly	Gly	Asn	Ala 1225	Ile	Leu	Glu	Asn	Ile 1230	Ser	Phe	Ser
Ile	Ser 1235	Pro	Gly	Gln	Arg	Val 1240	_	Leu	Leu	Gly	Arg 1245	Thr	Gly	Ser
Gly	Lys 1250		Thr	Leu	Leu	Ser 1255	Ala	Phe	Leu	Arg	Leu 1260	Leu	Asn	Thr
Glu	Gly 1265		Ile	Gln	Ile	Asp 1270		Val	Ser	Trp	Asp 1275	Ser	Ile	Thr
Leu	Gln 1280	Gln	Trp	Arg	Lys	Ala 1285	Phe	Gly	Val	Ile	Pro 1290	Gln	Lys	Val
Phe	Ile 1295		Ser	Gly	Thr	Phe 1300		Lys	Asn	Leu	Asp 1305	Pro	Tyr	Glu
Gln	Trp 1310	Ser	Asp	Gln	Glu	Ile 1315	Trp	Lys	Val	Ala	Asp 1320	Glu	Val	Gly
Leu	Arg 1325		Val	Ile	Glu	Gln 1330	Phe	Pro	Gly	Lys	Leu 1335	Asp	Phe	Val
	Val 1340													Leu
Met	Cys 1355	Leu	Ala	Arg	Ser	Val 1360	Leu	Ser	Lys	Ala	Lys 1365	Ile	Leu	Leu
Leu	Asp 1370		Pro	Ser	Ala	His 1375	Leu	Asp	Pro	Val	Thr 1380	Tyr	Gln	Ile
Ile	Arg 1385	Arg	Thr	Leu	Lys	Gln 1390	Ala	Phe	Ala	Asp	Cys 1395	Thr	Val	Ile
Leu	Cys	Glu	His	Arg	Ile	Glu	Ala	Met	Leu	Glu	Cys	Gln	Gln	Phe

1400 1405 1410

Leu Val Ile Glu Glu Asn Lys Val Arg Gln Tyr Asp Ser Ile Gln 1415 1420 1425

Lys Leu Leu Asn Glu Arg Ser Leu Phe Arg Gln Ala Ile Ser Pro 1430 1435 1440

Ser Asp Arg Val Lys Leu Phe Pro His Arg Asn Ser Ser Lys Cys 1445 1450 1455

Lys Ser Lys Pro Gln Ile Ala Ala Leu Lys Glu Glu Thr Glu Glu 1460 1465 1470

Glu Val Gln Asp Thr Arg Leu 1475 1480

<210> 136

<211> 502

<212> PRT

<213> Human

<400> 136

Met Leu Ala Ala Met Gly Ser Leu Ala Ala Ala Leu Trp Ala Val Val 1 5 10 15

His Pro Arg Thr Leu Leu Gly Thr Val Ala Phe Leu Leu Ala Ala 20 25 30

Asp Phe Leu Lys Arg Arg Pro Lys Asn Tyr Pro Pro Gly Pro Trp 35 40 45

Arg Leu Pro Phe Leu Gly Asn Phe Phe Leu Val Asp Phe Glu Gln Ser 50 55 60

His Leu Glu Val Gln Leu Phe Val Lys Lys Tyr Gly Asn Leu Phe Ser 65 70 75 80

Leu Glu Leu Gly Asp Ile Ser Ala Val Leu Ile Thr Gly Leu Pro Leu 85 90 95

Ile Lys Glu Ala Leu Ile His Met Asp Gln Asn Phe Gly Asn Arg Pro 100 105 110

Val Thr Pro Met Arg Glu His Ile Phe Lys Lys Asn Gly Leu Ile Met

115 120 125

Ser Ser Gly Gln Ala Trp Lys Glu Gln Arg Arg Phe Thr Leu Thr Ala 130 135 140

Leu Arg Asn Phe Gly Leu Gly Lys Lys Ser Leu Glu Glu Arg Ile Gln 145 150 155 160

Glu Glu Ala Gln His Leu Thr Glu Ala Ile Lys Glu Glu Asn Gly Gln 165 170 175

Pro Phe Asp Pro His Phe Lys Ile Asn Asn Ala Val Ser Asn Ile Ile 180 185 190

Cys Ser Ile Thr Phe Gly Glu Arg Phe Glu Tyr Gln Asp Ser Trp Phe 195 200 205

Gln Gln Leu Leu Lys Leu Leu Asp Glu Val Thr Tyr Leu Glu Ala Ser 210 215 220

Lys Thr Cys Gln Leu Tyr Asn Val Phe Pro Trp Ile Met Lys Phe Leu 225 230 235 240

Pro Gly Pro His Gln Thr Leu Phe Ser Asn Trp Lys Lys Leu Lys Leu 245 250 255

Phe Val Ser His Met Ile Asp Lys His Arg Lys Asp Trp Asn Pro Ala 260 265 270

Glu Thr Arg Asp Phe Ile Asp Ala Tyr Leu Lys Glu Met Ser Lys His 275 280 285

Thr Gly Asn Pro Thr Ser Ser Phe His Glu Glu Asn Leu Ile Cys Ser 290 295 300

Thr Leu Asp Leu Phe Phe Ala Gly Thr Glu Thr Thr Ser Thr Thr Leu 305 310 315 320

Arg Trp Ala Leu Leu Tyr Met Ala Leu Tyr Pro Glu Ile Gln Glu Lys 325 330 335

Val Gln Ala Glu Ile Asp Arg Val Ile Gly Gln Gly Gln Gln Pro Ser 340 345 350

Thr Ala Ala Arg Glu Ser Met Pro Tyr Thr Asn Ala Val Ile His Glu 355 360 365

Val Gln Arg Met Gly Asn Ile Ile Pro Leu Asn Val Pro Arg Glu Val 370 375 380

Thr Val Asp Thr Thr Leu Ala Gly Tyr His Leu Pro Lys Gly Thr Met 385 390 395 400

Ile Leu Thr Asn Leu Thr Ala Leu His Arg Asp Pro Thr Glu Trp Ala 405 410 415

Thr Pro Asp Thr Phe Asn Pro Asp His Phe Leu Glu Asn Gly Gln Phe 420 425 430

Lys Lys Arg Glu Ala Phe Met Pro Phe Ser Ile Gly Lys Arg Ala Cys 435 440 445

Leu Gly Glu Gln Leu Ala Arg Thr Glu Leu Phe Ile Phe Phe Thr Ser 450 455 460

Leu Met Gln Lys Phe Thr Phe Arg Pro Pro Asn Asn Glu Lys Leu Ser 465 470 475 480

Leu Lys Phe Arg Met Gly Ile Thr Ile Ser Pro Val Ser His Arg Leu 485 490 495

Cys Ala Val Pro Gln Val 500

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<400> 137

Met Lys Thr Pro Trp Arg Val Leu Leu Gly Leu Leu Gly Ala Ala Ala 1 5 10 15

Leu Val Thr Ile Ile Thr Val Pro Val Val Leu Leu Asn Lys Gly Thr 20 25 30

Asp Asp Ala Thr Ala Asp Ser Arg Lys Thr Tyr Thr Leu Thr Asp Tyr 35 40 45

313/439

Leu Lys Asn Thr Tyr Arg Leu Lys Leu Tyr Ser Leu Arg Trp Ile Ser 50 Asp His Glu Tyr Leu Tyr Lys Gln Glu Asn Asn Ile Leu Val Phe Asn 70 Ala Glu Tyr Gly Asn Ser Ser Val Phe Leu Glu Asn Ser Thr Phe Asp 85 Glu Phe Gly His Ser Ile Asn Asp Tyr Ser Ile Ser Pro Asp Gly Gln 105 Phe Ile Leu Leu Glu Tyr Asn Tyr Val Lys Gln Trp Arg His Ser Tyr Thr Ala Ser Tyr Asp Ile Tyr Asp Leu Asn Lys Arg Gln Leu Ile Thr Glu Glu Arg Ile Pro Asn Asn Thr Gln Trp Val Thr Trp Ser Pro Val Gly His Lys Leu Ala Tyr Val Trp Asn Asn Asp Ile Tyr Val Lys Ile 165 170 Glu Pro Asn Leu Pro Ser Tyr Arg Ile Thr Trp Thr Gly Lys Glu Asp 185 180 Ile Ile Tyr Asn Gly Ile Thr Asp Trp Val Tyr Glu Glu Val Phe 200 Ser Ala Tyr Ser Ala Leu Trp Trp Ser Pro Asn Gly Thr Phe Leu Ala 215 Tyr Ala Gln Phe Asn Asp Thr Glu Val Pro Leu Ile Glu Tyr Ser Phe Tyr Ser Asp Glu Ser Leu Gln Tyr Pro Lys Thr Val Arg Val Pro Tyr 245 Pro Lys Ala Gly Ala Val Asn Pro Thr Val Lys Phe Phe Val Val Asn 260 265 Thr Asp Ser Leu Ser Ser Val Thr Asn Ala Thr Ser Ile Gln Ile Thr 275 280 285

Ala Pro Ala Ser Met Leu Ile Gly Asp His Tyr Leu Cys Asp Val Thr 290 295 300 Trp Ala Thr Gln Glu Arg Ile Ser Leu Gln Trp Leu Arg Arg Ile Gln 305 310 Asn Tyr Ser Val Met Asp Ile Cys Asp Tyr Asp Glu Ser Ser Gly Arg 325 330 335 Trp Asn Cys Leu Val Ala Arg Gln His Ile Glu Met Ser Thr Thr Gly 340 345 350 Trp Val Gly Arg Phe Arg Pro Ser Glu Pro His Phe Thr Leu Asp Gly 355 360 365 Asn Ser Phe Tyr Lys Ile Ile Ser Asn Glu Glu Gly Tyr Arg His Ile 370 375 380 Cys Tyr Phe Gln Ile Asp Lys Lys Asp Cys Thr Phe Ile Thr Lys Gly 385 390 395 400 Thr Trp Glu Val Ile Gly Ile Glu Ala Leu Thr Ser Asp Tyr Leu Tyr Tyr Ile Ser Asn Glu Tyr Lys Gly Met Pro Gly Gly Arg Asn Leu Tyr Lys Ile Gln Leu Ser Asp Tyr Thr Lys Val Thr Cys Leu Ser Cys Glu 435 440 445 Leu Asn Pro Glu Arg Cys Gln Tyr Tyr Ser Val Ser Phe Ser Lys Glu 450 Ala Lys Tyr Tyr Gln Leu Arg Cys Ser Gly Pro Gly Leu Pro Leu Tyr 470 475 480 Thr Leu His Ser Ser Val Asn Asp Lys Gly Leu Arg Val Leu Glu Asp 485 490 495 Asn Ser Ala Leu Asp Lys Met Leu Gln Asn Val Gln Met Pro Ser Lys 500 505 510 Lys Leu Asp Phe Ile Ile Leu Asn Glu Thr Lys Phe Trp Tyr Gln Met 515 520 525

Ile Leu Pro Pro His Phe Asp Lys Ser Lys Lys Tyr Pro Leu Leu Leu 530 535 540

Asp Val Tyr Ala Gly Pro Cys Ser Gln Lys Ala Asp Ile Val Phe Arg 545 550 555 560

Leu Asn Trp Ala Thr Tyr Leu Ala Ser Thr Glu Asn Ile Ile Val Ala 565 570 575

Ser Phe Asp Gly Arg Gly Ser Gly Tyr Gln Gly Asp Lys Ile Met His 580 585 590

Ala Ile Asn Arg Arg Leu Gly Thr Phe Glu Val Glu Asp Gln Ile Glu 595 600 605

Ala Ala Arg Gln Phe Ser Lys Met Gly Phe Val Asp Asn Lys Arg Ile 610 615 620

Ala Ile Trp Gly Trp Ser Tyr Gly Gly Tyr Val Thr Ser Met Val Leu 625 630 635 640

Gly Ser Gly Ser Gly Val Phe Lys Cys Gly Ile Ala Val Ala Pro Val 645 650 655

Ser Arg Trp Glu Tyr Tyr Glu Ser Val Tyr Thr Glu Arg Tyr Met Gly 660 665 670

Leu Pro Thr Pro Glu Asp Asn Leu Asp His Tyr Arg Asn Ser Thr Val 675 680 685

Met Ser Arg Ala Glu Asn Phe Lys Gln Val Glu Tyr Leu Leu Ile His 690 695 700

Gly Thr Ala Asp Asp Asn Val His Phe Gln Gln Ser Ala Gln Ile Ser 705 710 715 720

Lys Ala Leu Val Asp Val Gly Val Asp Phe Gln Ala Met Trp Tyr Thr 725 730 735

Asp Glu Asp His Gly Ile Ala Ser Ser Thr Ala His Gln His Ile Tyr 740 745 750

Thr His Met Ser His Phe Ile Lys Gln Cys Phe Ser Leu Pro

765 760 755

<210> 138 <211> 984 <212> PRT <213> Human

<400> 138

Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu Val Leu Leu Cys 10

Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu Val Thr Leu Met Asp

Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro Pro Lys

Asp Gly Trp Ser Glu Gln Gln Gln Ile Leu Asn Gly Thr Pro Leu Tyr

Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp His Trp 70

Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg Val His

Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys Ser Phe Pro Gly Gly 105 100

Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn Leu Leu Tyr Met Glu 120 115

Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg Pro Leu Phe Gln Lys 135 130

Val Thr Thr Val Ala Ala Asp Gln Ser Phe Thr Ile Arg Asp Leu Ala 155 145

Ser Gly Ser Val Lys Leu Asn Val Glu Arg Cys Ser Leu Gly Arg Leu 165 170

Thr Arg Arg Gly Leu Tyr Leu Ala Phe His Asn Pro Gly Ala Cys Val 190 185 180

Ala Leu Val Ser Val Arg Val Phe Tyr Gln Arg Cys Pro Glu Thr Leu

195 200 205

Asn Gly Leu Ala Gln Phe Pro Asp Thr Leu Pro Gly Pro Ala Gly Leu 210 215 220

Val Glu Val Ala Gly Thr Cys Leu Pro His Ala Arg Ala Ser Pro Arg 225 230 235 240

Pro Ser Gly Ala Pro Arg Met His Cys Ser Pro Asp Gly Glu Trp Leu 245 250 255

Val Pro Val Gly Arg Cys His Cys Glu Pro Gly Tyr Glu Glu Gly Gly 260 265 270

Ser Gly Glu Ala Cys Val Ala Cys Pro Ser Gly Ser Tyr Arg Met Asp 275 280 285

Met Asp Thr Pro His Cys Leu Thr Cys Pro Gln Gln Ser Thr Ala Glu 290 295 300

Ser Glu Gly Ala Thr Ile Cys Thr Cys Glu Ser Gly His Tyr Arg Ala 305 310 315 320

Pro Gly Glu Gly Pro Gln Val Ala Cys Thr Gly Pro Pro Ser Ala Pro 325 330 335

Arg Asn Leu Ser Phe Ser Ala Ser Gly Thr Gln Leu Ser Leu Arg Trp 340 345 350

Glu Pro Pro Ala Asp Thr Gly Gly Arg Gln Asp Val Arg Tyr Ser Val 355 360 365

Arg Cys Ser Gln Cys Gln Gly Thr Ala Gln Asp Gly Gly Pro Cys Gln 370 375 380

Pro Cys Gly Val Gly Val His Phe Ser Pro Gly Ala Arg Ala Leu Thr 385 390 395 400

Thr Pro Ala Val His Val Asn Gly Leu Glu Pro Tyr Ala Asn Tyr Thr
405 410 415

Phe Asn Val Glu Ala Gln Asn Gly Val Ser Gly Leu Gly Ser Ser Gly 420 425 430

His Ala Ser Thr Ser Val Ser Ile Ser Met Gly His Ala Glu Ser Leu 435 440 445

Ser Gly Leu Ser Leu Arg Leu Val Lys Lys Glu Pro Arg Gln Leu Glu 450 455 460

Leu Thr Trp Ala Gly Ser Arg Pro Arg Ser Pro Gly Ala Asn Leu Thr 465 470 475 480

Tyr Glu Leu His Val Leu Asn Gln Asp Glu Glu Arg Tyr Gln Met Val 485 490 495

Leu Glu Pro Arg Val Leu Leu Thr Glu Leu Gln Pro Asp Thr Thr Tyr 500 505 510

Ile Val Arg Val Arg Met Leu Thr Pro Leu Gly Pro Gly Pro Phe Ser 515 520 525

Pro Asp His Glu Phe Arg Thr Ser Pro Pro Val Ser Arg Gly Leu Thr 530 535 540

Gly Gly Glu Ile Val Ala Val Ile Phe Gly Leu Leu Gly Ala Ala 545 550 555 560

Leu Leu Leu Gly Ile Leu Val Phe Arg Ser Arg Arg Ala Gln Arg Gln 565 570 575

Arg Gln Gln Arg His Val Thr Ala Pro Pro Met Trp Ile Glu Arg Thr 580 585 590

Ser Cys Ala Glu Ala Leu Cys Gly Thr Ser Arg His Thr Arg Thr Leu 595 600 605

His Arg Glu Pro Trp Thr Leu Pro Gly Gly Trp Ser Asn Phe Pro Ser 610 615 620

Arg Glu Leu Asp Pro Ala Trp Leu Met Val Asp Thr Val Ile Gly Glu 625 630 635 640

Gly Glu Phe Gly Glu Val Tyr Arg Gly Thr Leu Arg Leu Pro Ser Gln 645 650 655

Asp Cys Lys Thr Val Ala Ile Lys Thr Leu Lys Asp Thr Ser Pro Gly 660 665 670

Gly Gln Trp Trp Asn Phe Leu Arg Glu Ala Thr Ile Met Gly Gln Phe 680 Ser His Pro His Ile Leu His Leu Glu Gly Val Val Thr Lys Arg Lys Pro Ile Met Ile Ile Thr Glu Phe Met Glu Asn Ala Ala Leu Asp Ala 715 Phe Leu Arg Glu Arg Glu Asp Gln Leu Val Pro Gly Gln Leu Val Ala 730 Met Leu Gln Gly Ile Ala Ser Gly Met Asn Tyr Leu Ser Asn His Asn 740 745 Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Gln Asn 755 760 765 Leu Cys Cys Lys Val Ser Asp Phe Gly Leu Thr Arg Leu Leu Asp Asp 770 775 Phe Asp Gly Thr Tyr Glu Thr Gln Gly Gly Lys Ile Pro Ile Arg Trp 790 795 Thr Ala Pro Glu Ala Ile Ala His Arg Ile Phe Thr Thr Ala Ser Asp 805 810 Val Trp Ser Phe Gly Ile Val Met Trp Glu Val Leu Ser Phe Gly Asp 825 820 Lys Pro Tyr Gly Glu Met Ser Asn Gln Glu Val Met Lys Ser Ile Glu 835 840 845 Asp Gly Tyr Arg Leu Pro Pro Pro Val Asp Cys Pro Ala Pro Leu Tyr 850 855 860 Glu Leu Met Lys Asn Cys Trp Ala Tyr Asp Arg Ala Arg Arg Pro His 870 875 880 Phe Gln Lys Leu Gln Ala His Leu Glu Gln Leu Leu Ala Asn Pro His Ser Leu Arg Thr Ile Ala Asn Phe Asp Pro Arg Val Thr Leu Arg Leu 900 905

Pro Ser Leu Ser Gly Ser Asp Gly Ile Pro Tyr Arg Thr Val Ser Glu 915

Trp Leu Glu Ser Ile Arg Met Lys Arg Tyr Ile Leu His Phe His Ser 935

Ala Gly Leu Asp Thr Met Glu Cys Val Leu Glu Leu Thr Ala Glu Asp 950

Leu Thr Gln Met Gly Ile Thr Leu Pro Gly His Gln Lys Arg Ile Leu 970 965

Cys Ser Ile Gln Gly Phe Lys Asp 980

<210> 139 <211> 822 <212> PRT

<213> Human

<400> 139

Met Val Ser Trp Gly Arg Phe Ile Cys Leu Val Val Val Thr Met Ala 1 5

Thr Leu Ser Leu Ala Arg Pro Ser Phe Ser Leu Val Glu Asp Thr Thr 20 25

Leu Glu Pro Glu Glu Pro Pro Thr Lys Tyr Gln Ile Ser Gln Pro Glu 35

Val Tyr Val Ala Ala Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu 55 50

Lys Asp Ala Ala Val Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly 70 65

Pro Asn Asn Arg Thr Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly 90

Ala Thr Pro Arg Asp Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr 105 110 100

Val Asp Ser Glu Thr Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile 120 125 115

Ser	Ser 130	Gly	Asp	Asp	Glu	Asp 135	Asp	Thr	Asp	Gly	Ala 140	Glu	Asp	Phe	Val
Ser 145	Glu	Asn	Ser	Asn	Asn 150	Lys	Arg	Ala	Pro	Tyr 155	Trp	Thr	Asn	Thr	Glu 160
Lys	Met	Glu	Lys	Arg 165	Leu	His	Ala	Val	Pro 170	Ala	Ala	Asn	Thr	Val 175	Lys
Phe	Arg	Cys	Pro 180	Ala	Gly	Gly	Asn	Pro 185	Met	Pro	Thr	Met	Arg 190	Trp	Leu
Lys	Asn	Gly 195	Lys	Glu	Phe	Lys	Gln 200	Glu	His	Arg	Ile	Gly 205	Gly	Tyr	Lys
Val	Arg 210	Asn	Gln	His	Trp	Ser 215	Leu	Ile	Met	Glu	Ser 220	Val	Val	Pro	Ser
Asp 225	Lys	Gly	Asn	Tyr	Thr 230	Суѕ	Val	Val	Glu	Asn 235	Glu	Tyr	Gly	Ser	Ile 240
Asn	His	Thr	Tyr	His 245	Leu	Asp	Val	Val	Glu 250	Arg	Ser	Pro	His	Arg 255	Pro
Ile	Leu	Gln	Ala 260	Gly	Leu	Pro	Ala	Asn 265	Ala	Ser	Thr	Val	Val 270	Gly	Gly
Asp	Val	Glu 275	Phe	Val	Cys	Lys	Val 280	Tyr	Ser	Asp	Ala	Gln 285	Pro	His	Ile
Gln	Trp 290	Ile	Lys	Hìs	Val	Glu 295	Lys	Asn	Gly	Ser	Lys 300	Tyr	Gly	Pro	Asp
Gly 305	Leu	Pro	Tyr	Leu	Lys 310	Val	Leu	Lys	His	Ser 315	Gly	Ile	Asn	Ser	Ser 320
Asn	Ala	Glu	Val	Leu 325	Ala	Leu	Phe	Asn	Val 330	Thr	Glu	Ala	Asp	Ala 335	Gly
Glu	Tyr	Ile	Cys 340	Lys	Val	Ser	Asn	Tyr 345	Ile	Gly	Gln	Ala	Asn 350	Gln	Ser
Ala	Trp	Leu	Thr	Val	Leu	Pro	Lys	Gln	Gln	Ala	Pro	Gly	Arg	Glu	Lys

355 360 365

Glu Ile Thr Ala Ser Pro Asp Tyr Leu Glu Ile Ala Ile Tyr Cys Ile 370 375 380

Gly Val Phe Leu Ile Ala Cys Met Val Val Thr Val Ile Leu Cys Arg 385 390 395 400

Met Lys Asn Thr Thr Lys Lys Pro Asp Phe Ser Ser Gln Pro Ala Val 405 410 415

His Lys Leu Thr Lys Arg Ile Pro Leu Arg Arg Gln Val Thr Val Ser 420 425 430

Ala Glu Ser Ser Ser Ser Met Asn Ser Asn Thr Pro Leu Val Arg Ile 435 440 445

Thr Thr Arg Leu Ser Ser Thr Ala Asp Thr Pro Met Leu Ala Gly Val450 455 460

Ser Glu Tyr Glu Leu Pro Glu Asp Pro Lys Trp Glu Phe Pro Arg Asp 465 470 475 480

Lys Leu Thr Leu Gly Lys Pro Leu Gly Glu Gly Cys Phe Gly Gln Val 485 490 495

Val Met Ala Glu Ala Val Gly Ile Asp Lys Asp Lys Pro Lys Glu Ala 500 505 510

Val Thr Val Ala Val Lys Met Leu Lys Asp Asp Ala Thr Glu Lys Asp 515 520 525

Leu Ser Asp Leu Val Ser Glu Met Glu Met Met Lys Met Ile Gly Lys 530 535 540

His Lys Asn Ile Ile Asn Leu Leu Gly Ala Cys Thr Gln Asp Gly Pro 545 550 555 560

Leu Tyr Val Ile Val Glu Tyr Ala Ser Lys Gly Asn Leu Arg Glu Tyr
565 570 575

Leu Arg Ala Arg Arg Pro Pro Gly Met Glu Tyr Ser Tyr Asp Ile Asn 580 585 590

Arg	Val	Pro 595	Glu	Glu	Gln	Met	Thr 600	Phe	Lys	Asp	Leu	Val 605	Ser	Cys	Thr
Tyr	Gln 610	Leu	Ala	Arg	Gly	Met 615	Glu	Tyr	Leu	Ala	Ser 620	Gln	Lys	Cys	Ile
His 625	Arg	Asp	Leu	Ala	Ala 630	Arg	Asn	Val	Leu	Val 635	Thr	Glu	Asn	Asn	Val 640
Met	Lys	Ile	Ala	Asp 645	Phe	Gly	Leu	Ala	Arg 650	qaA	Ile	Asn	Asn	Ile 655	Asp
Tyr	Tyr	Lys	Lys 660	Thr	Thr	Asn	Gly	Arg 665	Leu	Pro	Val	Lys	Trp 670	Met	Ala
Pro	Glu	Ala 675	Leu	Phe	Asp	Arg	Val 680	Tyr	Thr	His	Gln	Ser 685	Asp	Val	Trp
Ser	Phe 690	Gly	Val	Leu	Met	Trp 695	Glu	Ile	Phe	Thr	Leu 700	Gly	Gly	Ser	Pro
Tyr 705	Pro	Gly	Ile	Pro	Val 710	Glu	Glu	Leu	Phe	Lys 715	Leu	Leu	Lys	Glu	Gly 720
His	Arg	Met	Asp	Lys 725	Pro	Ala	Asn	Cys	Thr 730	Asn	Glu	Leu	Tyr	Met 735	Met
Met	Arg	Asp	Cys 740	Trp	His	Ala	Val	Pro 745	Ser	Gln	Arg	Pro	Thr 750	Phe	Lys
Gln	Leu	Val 755	Glu				Arg 760		Leu	Thr	Leu	Thr 765	Thr	Asn	Glu
Glu	Tyr 770	Leu	Asp	Leu	Ser	Gln 775	Pro	Leu	Glu	Gln	Tyr 780	Ser	Pro	Ser	Tyr
Pro 785	Asp	Thr	Arg	Ser	Ser 790	Cys	Ser	Ser	Gly	Asp 795	Asp	Ser	Val	Phe	Ser 800
Pro	Asp	Pro	Met	Pro 805	Tyr	Glu	Pro	Cys	Leu 810	Pro	Gln	Tyr	Pro	His 815	Ile
Asn	Gly	Ser	Val 820	Lys	Thr										

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<211> 87

<212> PRT

<213> Human

<400> 140

Met Gln Lys Val Thr Leu Gly Leu Leu Val Phe Leu Ala Gly Phe Pro 1 5 10 15

Val Leu Asp Ala Asn Asp Leu Glu Asp Lys Asn Ser Pro Phe Tyr Tyr 20 25 30

Asp Trp His Ser Leu Gln Val Gly Gly Leu Ile Cys Ala Gly Val Leu $35 \hspace{1cm} 40 \hspace{1cm} 45$

Cys Ala Met Gly Ile Ile Ile Val Met Ser Ala Lys Cys Lys Cys Lys 50 55 60

Phe Gly Gln Lys Ser Gly His His Pro Gly Glu Thr Pro Pro Leu Ile 65 70 75 80

Thr Pro Gly Ser Ala Gln Ser 85

<210> 141

<211> 907

<212> PRT

<213> Human

<400> 141

Met Asp Thr Ser Arg Leu Gly Val Leu Leu Ser Leu Pro Val Leu Leu 1 5 10 15

Gln Leu Ala Thr Gly Gly Ser Ser Pro Arg Ser Gly Val Leu Leu Arg
20 25 30

Gly Cys Pro Thr His Cys His Cys Glu Pro Asp Gly Arg Met Leu Leu 35 40 45

Arg Val Asp Cys Ser Asp Leu Gly Leu Ser Glu Leu Pro Ser Asn Leu 50 55 60

Ser Val Phe Thr Ser Tyr Leu Asp Leu Ser Met Asn Asn Ile Ser Gln 65 70 75 80

Leu Leu Pro Asn Pro Leu Pro Ser Leu Arg Phe Leu Glu Glu Leu Arg Leu Ala Gly Asn Ala Leu Thr Tyr Ile Pro Lys Gly Ala Phe Thr Gly Leu Tyr Ser Leu Lys Val Leu Met Leu Gln Asn Asn Gln Leu Arg His 120 Val Pro Thr Glu Ala Leu Gln Asn Leu Arg Ser Leu Gln Ser Leu Arg 135 Leu Asp Ala Asn His Ile Ser Tyr Val Pro Pro Ser Cys Phe Ser Gly 150 155 Leu His Ser Leu Arg His Leu Trp Leu Asp Asp Asn Ala Leu Thr Glu 165 170 Ile Pro Val Gln Ala Phe Arg Ser Leu Ser Ala Leu Gln Ala Met Thr 180 185 Leu Ala Leu Asn Lys Ile His His Ile Pro Asp Tyr Ala Phe Gly Asn 200 Leu Ser Ser Leu Val Val Leu His Leu His Asn Asn Arg Ile His Ser Leu Gly Lys Lys Cys Phe Asp Gly Leu His Ser Leu Glu Thr Leu Asp 225 230 235 Leu Asn Tyr Asn Asn Leu Asp Glu Phe Pro Thr Ala Ile Arg Thr Leu 245 250 Ser Asn Leu Lys Glu Leu Gly Phe His Ser Asn Asn Ile Arg Ser Ile 260 265 Pro Glu Lys Ala Phe Val Gly Asn Pro Ser Leu Ile Thr Ile His Phe 275 280 285 Tyr Asp Asn Pro Ile Gln Phe Val Gly Arg Ser Ala Phe Gln His Leu 290 295 300 Pro Glu Leu Arg Thr Leu Thr Leu Asn Gly Ala Ser Gln Ile Thr Glu 305 310 315

Phe	Pro	Asp	Leu	Thr 325	Gly	Thr	Ala	Asn	Leu 330	Glu	Ser	Leu	Thr	Leu 335	Thr
Gly	Ala	Gln	Ile 340	Ser	Ser	Leu	Pro	Gln 345	Thr	Val	Суз	Asn	Gln 350	Leu	Pro
Asn	Leu	Gln 355	Val	Leu	Asp	Leu	Ser 360	Tyr	Asn	Leu	Leu	Glu 365	Asp	Leu	Pro
Ser	Phe 370	Ser	Val	Cys	Gln	Lys 375	Leu	Gln	Lys	Ile	Asp 380	Leu	Arg	His	Asn
Glu 385	Ile	Tyr	Glu	Ile	Lys 390	Val	Asp	Thr	Phe	Gln 395	Gln	Leu	Leu	Ser	Leu 9
Arg	Ser	Leu	Asn	Leu 405	Ala	Trp	Asn	Lys	Ile 410	Ala	Ile	Ile	His	Pro 415	Asn
Ala	Phe	Ser	Thr 420	Leu	Pro	Ser	Leu	Ile 425	Lys	Leu	Asp	Leu	Ser 430	Ser	Asn
Leu	Leu	Ser 435		Phe	Pro	Ile	Thr 440	Gly	Leu	His	Gly	Leu 445	Thr	His	Leu
Lys	Leu 450		Gly	Asn	His	Ala 455	Leu	Gln	Ser	Leu	Ile 460	Ser	Ser	Glu	Asn
Phe 465		Glu	Leu	Lys	Val 470		Glu	Met	Pro	Tyr 475	Ala	Tyr	Gln	Cys	Cys 480
Ala	Phe	Gly					Ala				Ser	Asn	Gln	Trp 495	Asn
Lys	Gly	Asp	Asn 500		Ser	Met	Asp	Asp 505		His	Lys	Lys	Asp 510		Gly
Met	Phe	Gln 515		Gln	. Asp	Glu	Arg 520		Leu	Glu	Asp	Phe 525	Leu	. Leu	Asp
Phe	: Glu 530		ı Asp	Leu	. Lys	Ala 535		His	Ser	· Val	Gln 540		Ser	· Pro	Ser
Pro 545	_	7 Pro) Phe	. Lys	9rc 550		: Glu	ı His	Leu	Leu 555		Gly	Trp	Leu	Ile 560

Arg Ile Gly Val Trp Thr Ile Ala Val Leu Ala Leu Thr Cys Asn Ala 565 570 575

Leu Val Thr Ser Thr Val Phe Arg Ser Pro Leu Tyr Ile Ser Pro Ile 580 585 590

Lys Leu Leu Ile Gly Val Ile Ala Ala Val Asn Met Leu Thr Gly Val 595 600 605

Ser Ser Ala Val Leu Ala Gly Val Asp Ala Phe Thr Phe Gly Ser Phe 610 615 620

Ala Arg His Gly Ala Trp Trp Glu Asn Gly Val Gly Cys His Val Ile 625 630 635 640

Gly Phe Leu Ser Ile Phe Ala Ser Glu Ser Ser Val Phe Leu Leu Thr 645 650 655

Leu Ala Ala Leu Glu Arg Gly Phe Ser Val Lys Tyr Ser Ala Lys Phe 660 665 670

Glu Thr Lys Ala Pro Phe Ser Ser Leu Lys Val Ile Ile Leu Leu Cys 675 680 685

Ala Leu Leu Ala Leu Thr Met Ala Ala Val Pro Leu Gly Gly Ser 690 695 700

Lys Tyr Gly Ala Ser Pro Leu Cys Leu Pro Leu Pro Phe Gly Glu Pro 705 710 715 720

Ser Thr Met Gly Tyr Met Val Ala Leu Ile Leu Leu Asn Ser Leu Cys 725 730 735

Phe Leu Met Met Thr Ile Ala Tyr Thr Lys Leu Tyr Cys Asn Leu Asp 740 745 750

Lys Gly Asp Leu Glu Asn Ile Trp Asp Cys Ser Met Val Lys His Ile 755 760 765

Ala Leu Leu Leu Phe Thr Asn Cys Ile Leu Asn Cys Pro Val Ala Phe 770 775 780

Leu Ser Phe Ser Ser Leu Ile Asn Leu Thr Phe Ile Ser Pro Glu Val

785 790 795 800

Ile Lys Phe Ile Leu Leu Val Val Val Pro Leu Pro Ala Cys Leu Asn 805 810 815

Pro Leu Leu Tyr Ile Leu Phe Asn Pro His Phe Lys Glu Asp Leu Val 820 825 830

Ser Leu Arg Lys Gln Thr Tyr Val Trp Thr Arg Ser Lys His Pro Ser 835 840 845

Leu Met Ser Ile Asn Ser Asp Asp Val Glu Lys Gln Ser Cys Asp Ser 850 860

Thr Gln Ala Leu Val Thr Phe Thr Ser Ser Ser Ile Thr Tyr Asp Leu 865 870 875 880

Pro Pro Ser Ser Val Pro Ser Pro Ala Tyr Pro Val Thr Glu Ser Cys 885 890 895

His Leu Ser Ser Val Ala Phe Val Pro Cys Leu 900 905

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<211> 1134

<212> PRT

<213> Human

<400> 142

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Thr Ala Pro Glu Asn Gly Ile Val Arg Gln Glu Pro Gly Ser Pro Pro 20 25 30

Arg Asp Gly Leu His His Gly Pro Leu Cys Leu Gly Glu Pro Ala Pro 35 40 45

Phe Trp Arg Gly Val Leu Ser Thr Pro Asp Ser Trp Leu Pro Pro Gly 50 55 60

Phe Pro Gln Gly Pro Lys Asp Met Leu Pro Leu Val Glu Gly Glu Gly 65 70 75 80

Pro Gln Asn Gly Glu Arg Lys Val Asn Trp Leu Gly Ser Lys Glu Gly

90 95

Leu Arg Trp Lys Glu Ala Met Leu Thr His Pro Leu Ala Phe Cys Gly 100 105 110

Pro Ala Cys Pro Pro Arg Cys Gly Pro Leu Met Pro Glu Hìs Ser Gly 115 120 125

Gly His Leu Lys Ser Asp Pro Val Ala Phe Arg Pro Trp His Cys Pro 130 135 140

Phe Leu Leu Glu Thr Lys Ile Leu Glu Arg Ala Pro Phe Trp Val Pro 145 150 155 160

Thr Cys Leu Pro Pro Tyr Leu Val Ser Gly Leu Pro Pro Glu His Pro 165 170 175

Cys Asp Trp Pro Leu Thr Pro His Pro Trp Val Tyr Ser Gly Gln 180 185 190

Pro Lys Val Pro Ser Ala Phe Ser Leu Gly Ser Lys Gly Phe Tyr Tyr 195 200 205

Lys Asp Pro Ser Ile Pro Arg Leu Ala Lys Glu Pro Leu Ala Ala Ala 210 215 220

Glu Pro Gly Leu Phe Gly Leu Asn Ser Gly Gly His Leu Gln Arg Ala 225 230 235 240

Gly Glu Ala Glu Arg Pro Ser Leu His Gln Arg Asp Gly Glu Met Gly 245 250 255

Ala Gly Arg Gln Gln Asn Pro Cys Pro Leu Phe Leu Gly Gln Pro Asp 260 265 270

Thr Val Pro Trp Thr Ser Trp Pro Ala Cys Pro Pro Gly Leu Val His 275 280 285

Thr Leu Gly Asn Val Trp Ala Gly Pro Gly Asp Gly Asn Leu Gly Tyr 290 295 300

Gln Leu Gly Pro Pro Ala Thr Pro Arg Cys Pro Ser Pro Glu Pro Pro 305 310 315 320

Val Thr Gln Arg Gly Cys Cys Ser Ser Tyr Pro Pro Thr Lys Gly Gly 325 330 Gly Leu Gly Pro Cys Gly Lys Cys Gln Glu Gly Leu Glu Gly Gly Ala 345 340 Ser Gly Ala Ser Glu Pro Ser Glu Glu Val Asn Lys Ala Ser Gly Pro 360 Arq Ala Cys Pro Pro Ser His His Thr Lys Leu Lys Lys Thr Trp Leu 375 Thr Arg His Ser Glu Gln Phe Glu Cys Pro Arg Gly Cys Pro Glu Val 395 Glu Glu Arg Pro Val Ala Arg Leu Arg Ala Leu Lys Arg Ala Gly Ser 410 Pro Glu Val Gln Gly Ala Met Gly Ser Pro Ala Pro Lys Arg Pro Pro Asp Pro Phe Pro Gly Thr Ala Glu Gln Gly Ala Gly Gly Trp Gln Glu 440 Val Arg Asp Thr Ser Ile Gly Asn Lys Asp Val Asp Ser Gly Gln His 455 Asp Glu Gln Lys Gly Pro Gln Asp Gly Gln Ala Ser Leu Gln Asp Pro 470 475 Gly Leu Gln Asp Ile Pro Cys Leu Ala Leu Pro Ala Lys Leu Ala Gln 485 490 Cys Gln Ser Cys Ala Gln Ala Ala Gly Glu Gly Gly His Ala Cys 500 505 His Ser Gln Gln Val Arg Arg Ser Pro Leu Gly Gly Glu Leu Gln Gln 515 520 Glu Glu Asp Thr Ala Thr Asn Ser Ser Glu Glu Gly Pro Gly Ser 530 535 Gly Pro Asp Ser Arg Leu Ser Thr Gly Leu Ala Lys His Leu Leu Ser 545 550 555

Gly Leu Gly Asp Arg Leu Cys Arg Leu Leu Arg Arg Glu Arg Glu Ala Leu Ala Trp Ala Gln Arg Glu Gly Gln Gly Pro Ala Val Thr Glu Asp Ser Pro Gly Ile Pro Arg Cys Cys Ser Arg Cys His His Gly Leu Phe Asn Thr His Trp Arg Cys Pro Arg Cys Ser His Arg Leu Cys Val Ala Cys Gly Arg Val Ala Gly Thr Gly Arg Ala Arg Glu Lys Ala Gly Phe Gln Glu Gln Ser Ala Glu Glu Cys Thr Gln Glu Ala Gly His Ala Ala Cys Ser Leu Met Leu Thr Gln Phe Val Ser Ser Gln Ala Leu Ala Glu Leu Ser Thr Ala Met His Gln Val Trp Val Lys Phe Asp Ile Arg Gly His Cys Pro Cys Gln Ala Asp Ala Arg Val Trp Ala Pro Gly Asp Ala Gly Gln Gln Lys Glu Ser Thr Gln Lys Thr Pro Pro Thr Pro Gln Pro Ser Cys Asn Gly Asp Thr His Arg Thr Lys Ser Ile Lys Glu Glu Thr Pro Asp Ser Ala Glu Thr Pro Ala Glu Asp Arg Ala Gly Arg Gly Pro Leu Pro Cys Pro Ser Leu Cys Glu Leu Leu Ala Ser Thr Ala Val Lys Leu Cys Leu Gly His Glu Arg Ile His Met Ala Phe Ala Pro Val Thr Pro Ala Leu Pro Ser Asp Asp Arg Ile Thr Asn Ile Leu Asp Ser Ile

Ile Ala Gln Val Val Glu Arg Lys Ile Gln Glu Lys Ala Leu Gly Pro 805 810 815

- Gly Leu Arg Ala Gly Pro Gly Leu Arg Lys Gly Leu Gly Leu Pro Leu 820 825 830
- Ser Pro Val Arg Pro Arg Leu Pro Pro Pro Gly Ala Leu Leu Trp Leu 835 840 845
- Gln Glu Pro Gln Pro Cys Pro Arg Arg Gly Phe His Leu Phe Gln Glu 850 855 860
- His Trp Arg Gln Gly Gln Pro Val Leu Val Ser Gly Ile Gln Arg Thr 865 870 875 880
- Leu Gln Gly Asn Leu Trp Gly Thr Glu Ala Leu Gly Ala Leu Gly Gly 885 890 895
- Gln Val Gln Ala Leu Ser Pro Leu Gly Pro Pro Gln Pro Ser Ser Leu 900 905 910
- Gly Ser Thr Thr Phe Trp Glu Gly Phe Ser Trp Pro Glu Leu Arg Pro 915 920 925
- Lys Ser Asp Glu Gly Ser Val Leu Leu Leu His Arg Ala Leu Gly Asp 930 935 940
- Glu Asp Thr Ser Arg Val Glu Asn Leu Ala Ala Ser Leu Pro Leu Pro 945 950 955 960
- Glu Tyr Cys Ala Leu His Gly Lys Leu Asn Leu Ala Ser Tyr Leu Pro $965 \hspace{1.5cm} 970 \hspace{1.5cm} 975$
- Pro Gly Leu Ala Leu Arg Pro Leu Glu Pro Gln Leu Trp Ala Ala Tyr 980 985 990
- Gly Val Ser Pro His Arg Gly His Leu Gly Thr Lys Asn Leu Cys Val 995 1000 1005
- Glu Val Ala Asp Leu Val Ser Ile Leu Val His Ala Asp Thr Pro 1010 1015 1020
- Leu Pro Ala Trp His Arg Ala Gln Lys Asp Phe Leu Ser Gly Leu

1025 1030 1035

Asp Gly Glu Gly Leu Trp Ser Pro Gly Ser Gln Val Ser Thr Val 1040 1040 1050

Trp His Val Phe Arg Ala Gln Asp Ala Gln Arg Ile Arg Arg Phe 1055 1060 1065

Leu Gln Met Val Gln Gly Leu Val Ser Thr Val Ser Val Thr Gln 1070 1075 1080

His Phe Leu Ser Pro Glu Thr Ser Ala Leu Ser Ala Gln Leu Cys 1085

His Gln Gly Pro Ser Leu Pro Pro Asp Cys His Leu Leu Tyr Ala 1100 1105 1110

Gln Met Asp Trp Ala Val Phe Gln Ala Val Lys Val Ala Val Gly 1115 1120 1125

Thr Leu Gln Glu Ala Lys 1130

<210> 143

<211> 142

<212> PRT

<213> Human

<400> 143

Met Val Leu Ser Pro Ala Asp Lys Thr Asn Val Lys Ala Ala Trp Gly 1 5 10 15

Lys Val Gly Ala His Ala Gly Glu Tyr Gly Ala Glu Ala Leu Glu Arg 20 25 30

Met Phe Leu Ser Phe Pro Thr Thr Lys Thr Tyr Phe Pro His Phe Asp 35 40 45

Leu Ser His Gly Ser Ala Gln Val Lys Gly His Gly Lys Lys Val Ala 50 55 60

Asp Ala Leu Thr Asn Ala Val Ala His Val Asp Asp Met Pro Asn Ala 65 70 75 80

Leu Ser Ala Leu Ser Asp Leu His Ala His Lys Leu Arg Val Asp Pro

90 95

Val Asn Phe Lys Leu Leu Ser His Cys Leu Leu Val Thr Leu Ala Ala 100 105 110

His Leu Pro Ala Glu Phe Thr Pro Ala Val His Ala Ser Leu Asp Lys 115 120 125

Phe Leu Ala Ser Val Ser Thr Val Leu Thr Ser Lys Tyr Arg 130 135 140

<210> 144

<211> 543

<212> PRT

<213> Human

<400> 144

Met Leu Leu Arg Ser Lys Pro Ala Leu Pro Pro Pro Leu Met Leu Leu 1 5 10 15

Leu Leu Gly Pro Leu Gly Pro Leu Ser Pro Gly Ala Leu Pro Arg Pro
20 25 30

Ala Gln Ala Gln Asp Val Val Asp Leu Asp Phe Phe Thr Gln Glu Pro 35 40 45

Leu His Leu Val Ser Pro Ser Phe Leu Ser Val Thr Ile Asp Ala Asn 50 55 60

Leu Ala Thr Asp Pro Arg Phe Leu Ile Leu Leu Gly Ser Pro Lys Leu 65 70 75 80

Arg Thr Leu Ala Arg Gly Leu Ser Pro Ala Tyr Leu Arg Phe Gly Gly 85 90 95

Thr Lys Thr Asp Phe Leu Ile Phe Asp Pro Lys Lys Glu Ser Thr Phe 100 105 110

Glu Glu Arg Ser Tyr Trp Gln Ser Gln Val Asn Gln Asp Ile Cys Lys 115 120 125

Tyr Gly Ser Ile Pro Pro Asp Val Glu Glu Lys Leu Arg Leu Glu Trp 130 135 140

Pro Tyr Gln Glu Gln Leu Leu Leu Arg Glu His Tyr Gln Lys Lys Phe

145 150 155 160 Lys Asn Ser Thr Tyr Ser Arg Ser Ser Val Asp Val Leu Tyr Thr Phe 170 Ala Asn Cys Ser Gly Leu Asp Leu Ile Phe Gly Leu Asn Ala Leu Leu 185 Arg Thr Ala Asp Leu Gln Trp Asn Ser Ser Asn Ala Gln Leu Leu 200 Asp Tyr Cys Ser Ser Lys Gly Tyr Asn Ile Ser Trp Glu Leu Gly Asn 215 Glu Pro Asn Ser Phe Leu Lys Lys Ala Asp Ile Phe Ile Asn Gly Ser 230 235 Gln Leu Gly Glu Asp Phe Ile Gln Leu His Lys Leu Leu Arg Lys Ser 245 250 Thr Phe Lys Asn Ala Lys Leu Tyr Gly Pro Asp Val Gly Gln Pro Arg 260 Arg Lys Thr Ala Lys Met Leu Lys Ser Phe Leu Lys Ala Gly Gly Glu 275 Val Ile Asp Ser Val Thr Trp His His Tyr Tyr Leu Asn Gly Arg Thr 290 295 300 Ala Thr Arg Glu Asp Phe Leu Asn Pro Asp Val Leu Asp Ile Phe Ile 305 Ser Ser Val Gln Lys Val Phe Gln Val Val Glu Ser Thr Arg Pro Gly 325 Lys Lys Val Trp Leu Gly Glu Thr Ser Ser Ala Tyr Gly Gly Gly Ala 340 345 Pro Leu Leu Ser Asp Thr Phe Ala Ala Gly Phe Met Trp Leu Asp Lys 355 360

· Leu Gly Leu Ser Ala Arg Met Gly Ile Glu Val Val Met Arg Gln Val

370

Phe 385	Phe	Gly	Ala	Gly	Asn 390	Tyr	His	Leu	Val	Asp 395	Glu	Asn	Phe	Asp	Pro 400
Leu	Pro	Asp	Tyr	Trp 405	Leu	Ser	Leu	Leu	Phe 410	Lys	Lys	Leu	Val	Gly 415	Thr
Lys	Val	Leu	Met 420	Ala	Ser	Val	Gln	Gly 425	Ser	Lys	Arg	Arg	Lys 430	Leu	Arg
Val	Tyr	Leu 435	His	Cys	Thr	Asn	Thr 440	Asp	Asn	Pro	Arg	Tyr 445	Lys	Glu	Gly
Asp	Leu 450	Thr	Leu	Tyr	Ala	Ile 455	Asn	Leu	His	Asn	Val 460	Thr	Lys	Tyr	Leu
Arg 465	Leu	Pro	Tyr	Pro	Phe 470	Ser	Asn	Lys	Gln	Val 475	Asp	Lys	Tyr	Leu	Leu 480
Arg	Pro	Leu	Gly	Pro 485	His	Gly	Leu	Leu	Ser 490	Lys	Ser	Val	Gln	Leu 495	Asn
Gly	Leu	Thr	Leu 500	Lys	Met	Val	Asp	Asp 505	Gln	Thr	Leu	Pro	Pro 510	Leu	Met
Glu	Lys	Pro 515	Leu	Arg	Pro	Gly	Ser 520		Leu	Gly	Leu	Pro 525	Ala	Phe	Ser
Tyr	Ser 530	Phe	Phe	Val	Ile	Arg 535	Asn	Ala	Lys	Val	Ala 540	Ala	Cys	Ile	
<210 <210 <210 <210	1> : 2> :	145 203 PRT Human	n												
<400)> :	145													
Cys 1	Ser	Val	Pro	Phe 5	Leu	Pro	Leu	Ala	Val 10	Pro	Val	Arg	Ala	Val 15	His
Arg	Leu	Leu	Glu 20	His	Arg	His	His	Ser 25	Val	Thr	Trp	Pro	Ala 30	Thr	Glu
Leu	Pro	Ile 35	Thr	Gln	Leu	Thr	Ser 40	Ser	Ile	Val	Arg	Arg 45	Val	Asn	Glu

Ala Ser Gly Leu Tyr Gln Met Phe Gly Val Leu Ala Asp Val Ile Leu 50 55 60

Leu Lys Glu Thr Gly Gly Glu Val Pro Pro Cys Thr Leu Ala Pro Ala 65 70 75 80

Ser Ala His Gly His Pro Ser His Arg Gly Arg Leu Leu Asn Arg Leu 85 90 95

Asp Cys Pro Asp Arg Ala His Pro Thr Ser Glu Ala Leu Pro Gly Glu 100 105 110

Leu Phe Gly His Arg Phe Ala Lys Leu Leu Cys Arg Val Leu Leu Pro 115 120 125

Val Arg Pro His Ala Pro Glu Val Ala Thr Leu Leu Pro Ala Gly Val 130 135 140

Pro Glu Asp Ala Gly Thr Arg Glu Tyr Arg Glu Pro Leu Ala Ala Gln 145 150 155 160

Ser Gly Glu Gln Ala Pro Ala Gly Leu Cys Pro His Arg Gln Ala Pro 165 170 175

Gly Gly Gln Gln Pro Ala Ala Trp Arg Pro Arg Ala Thr Arg Phe Pro 180 185 190

Pro Gly Ser Arg Ala Ser Gly Ser Val Arg Arg 195 200

<210> 146

<211> 414

<212> PRT

<213> Human

<400> 146

Met Lys Ala Gln Thr Ala Leu Ser Phe Phe Leu Ile Leu Ile Thr Ser 1 5 10 15

Leu Ser Gly Ser Gln Gly Ile Phe Pro Leu Ala Phe Phe Ile Tyr Val $20 \hspace{1.5cm} 25 \hspace{1.5cm} 30$

Pro Met Asn Glu Gln Ile Val Ile Gly Arg Leu Asp Glu Asp Ile Ile 35 40 45

Leu Pro Ser Ser Phe Glu Arg Gly Ser Glu Val Val Ile His Trp Lys 50 55 60

Tyr Gln Asp Ser Tyr Lys Val His Ser Tyr Tyr Lys Gly Ser Asp His 65 70 75 80

Leu Glu Ser Gln Asp Pro Arg Tyr Ala Asn Arg Thr Ser Leu Phe Tyr 85 90 95

Asn Glu Ile Gln Asn Gly Asn Ala Ser Leu Phe Phe Arg Arg Val Ser 100 105 110

Leu Leu Asp Glu Gly Ile Tyr Thr Cys Tyr Val Gly Thr Ala Ile Gln 115 120 125

Val Ile Thr Asn Lys Val Val Leu Lys Val Gly Val Phe Leu Thr Pro 130 135 140

Val Met Lys Tyr Glu Lys Arg Asn Thr Asn Ser Phe Leu Ile Cys Ser 145 150 155 160

Val Leu Ser Val Tyr Pro Arg Pro Ile Ile Thr Trp Lys Met Asp Asn 165 170 175

Thr Pro Ile Ser Glu Asn Asn Met Glu Glu Thr Gly Ser Leu Asp Ser 180 185 190

Phe Ser Ile Asn Ser Pro Leu Asn Ile Thr Gly Ser Asn Ser Ser Tyr 195 200 205

Glu Cys Thr Ile Glu Asn Ser Leu Leu Lys Gln Thr Trp Thr Gly Arg 210 215 220

Trp Thr Met Lys Asp Gly Leu His Lys Met Gln Ser Glu His Val Ser 225 230 235 240

Leu Ser Cys Gln Pro Val Asn Asp Tyr Phe Ser Pro Asn Gln Asp Phe 245 250 255

Lys Val Thr Trp Ser Arg Met Lys Ser Gly Thr Phe Ser Val Leu Ala 260 265 270

Tyr Tyr Leu Ser Ser Ser Gln Asn Thr Ile Ile Asn Glu Ser Arg Phe 275 280 285

Ser Trp Asn Lys Glu Leu Ile Asn Gln Ser Asp Phe Ser Met Asn Leu 290 295 300

Met Asp Leu Asn Leu Ser Asp Ser Gly Glu Tyr Leu Cys Asn Ile Ser 305 310 315 320

Ser Asp Glu Tyr Thr Leu Leu Thr Ile His Thr Val His Val Glu Pro 325 330 335

Ser Gln Glu Thr Ala Ser His Asn Lys Gly Leu Trp Ile Leu Val Pro 340 345 350

Ser Ala Ile Leu Ala Ala Phe Leu Leu Ile Trp Ser Val Lys Cys Cys 355 360 365

Arg Ala Gln Leu Glu Ala Arg Arg Ser Arg His Pro Ala Asp Gly Ala 370 375 380

Gln Gln Glu Arg Cys Cys Val Pro Pro Gly Glu Arg Cys Pro Ser Ala 385 390 395 400

Pro Asp Asn Gly Glu Glu Asn Val Pro Leu Ser Gly Lys Val 405 410

<210> 147

<211> 545

<212> PRT

<213> Human

<400> 147

Met Val Asp Ala Ala Glu Asn Leu Cys Pro Asn Val Met Lys Lys Ala 1 5 10 15

His Ile Arg Gln Asp Leu Ile His Ala Ser Thr Glu Lys Ile Ser Ile 20 25 30

Pro Arg Thr Phe Val Lys Asn Val Leu Leu Glu Gln Ser Gly Ile Asp 35 40 45

Ile Leu Asn Lys Ile Ser Glu Val Lys Leu Thr Val Ala Ser Phe Leu 50 55 60

Ser Asp Arg Ile Val Asp Glu Ile Leu Asp Ala Leu Ser His Cys His 65 70 75 80

His Lys Leu Ala Asp His Phe Ser Arg Arg Gly Lys Thr Leu Pro Gln 90 Gln Glu Ser Leu Glu Ile Glu Leu Ala Glu Glu Arg Pro Val Lys Arg Ser Ile Ile Thr Val Glu Glu Leu Thr Glu Ile Glu Arg Leu Glu Asp 115 120 Leu Asp Thr Cys Met Met Thr Pro Lys Ser Lys Arg Lys Ser Ile His Ser Arg Met Leu Arg Pro Val Ser Arg Ala Phe Glu Met Glu Phe Asp 155 Leu Asp Lys Ala Leu Glu Glu Val Pro Ile His Ile Glu Asp Pro Pro 170 Phe Pro Ser Leu Arg Gln Glu Lys Arg Ser Ser Gly Phe Ile Ser Glu 185 Leu Pro Ser Glu Glu Gly Lys Lys Leu Glu His Phe Thr Lys Leu Arg 200 Pro Lys Arg Asn Lys Lys Gln Gln Pro Thr Gln Ala Ala Val Cys Ala 210 215 Ala Asn Ile Val Ser Gln Asp Gly Glu Gln Asn Gly Leu Met Gly Arg 230 Val Asp Glu Gly Val Asp Glu Phe Phe Thr Lys Lys Val Thr Lys Met 245 Asp Ser Lys Lys Trp Ser Thr Arg Gly Ser Glu Ser His Glu Leu Asn 260 Glu Gly Gly Asp Glu Lys Lys Lys Arg Asp Ser Arg Lys Ser Ser Gly 275 Phe Leu Asn Leu Ile Lys Ser Arg Ser Lys Ser Glu Arg Pro Pro Thr 290 Ile Leu Met Thr Glu Glu Pro Ser Ser Pro Lys Gly Ala Val Arg Ser 305 310 315

Pro	Pro	Val	Asp	Cys 325	Pro	Arg	Lys	Asp	Thr 330	Lys	Ala	Ala	Glu	His 335	Asn
Gly	Asn	Ser	Glu 340	Arg	Ile	Glu	Glu	Ile 345	Lys	Thr	Pro	Asp	Ser 350	Phe	Glu
Glu	Ser	Gln 355	Gly	Glu	Glu	Ile	Gly 360	Lys	Val	Glu	Arg	Ser 365	Asp	Ser	Lys
Ser	Ser 370	Pro	Gln	Ala	Gly	Arg 375	Arg	Tyr	Gly	Val	Gln 380	Val	Met	Gly	Ser
Gly 385	Leu	Leu	Ala	Glu	Met 390	Lys	Ala	Lys	Gln	Glu 395	Asn	Arg	Phe	Gly	Leu 400
Gly	Thr	Pro	Glu	Lys 405	Asn	Thr	Lys	Ala	Glu 410	Pro	Lys	Ala	Glu	Ala 415	Gly
Ser	Arg	Ser	Arg 420	Ser	Ser	Ser	Ser	Thr 425	Pro	Thr	Ser	Pro	Lys 430	Pro	Leu
		435	Pro				440					445			
1	450		Thr			455					4,60				
465			Val		470					475		_			480
			Arg	485					490					495	
			Glu 500					505		_			510		
		515	Gln				520					525			
ser	Lys 530	ser	Asn	Asp	ser	Gly 535	GLU	GLU	Ala	GLu	Lys 540	GLu	Phe	Ile	Phe

Val

545

<210> 148

<211> 315 <212> PRT

<213> Human

<400> 148

Met Pro Leu Lys Leu Arg Gly Lys Lys Lys Ala Lys Ser Lys Glu Thr 10

Ala Gly Leu Val Glu Gly Glu Pro Thr Gly Ala Gly Gly Ser Leu

Ser Ala Ser Arg Ala Pro Ala Arg Arg Leu Val Phe His Ala Gln Leu

Ala His Gly Ser Ala Thr Gly Arg Val Glu Gly Phe Ser Ser Ile Gln

Glu Leu Tyr Ala Gln Ile Ala Gly Ala Phe Glu Ile Ser Pro Ser Glu

Ile Leu Tyr Cys Thr Leu Asn Thr Pro Lys Ile Asp Met Glu Arg Leu 90

Leu Gly Gly Gln Leu Gly Leu Glu Asp Phe Ile Phe Ala His Val Lys 105

Gly Ile Glu Lys Glu Val Asn Val Tyr Lys Ser Glu Asp Ser Leu Gly 120

Leu Thr Ile Thr Asp Asn Gly Val Gly Tyr Ala Phe Ile Lys Arg Ile 135

Lys Asp Gly Gly Val Ile Asp Ser Val Lys Thr Ile Cys Val Gly Asp 150

His Ile Glu Ser Ile Asn Gly Glu Asn Ile Val Gly Trp Arg His Tyr

Asp Val Ala Lys Lys Leu Lys Glu Leu Lys Lys Glu Glu Leu Phe Thr 180 185 190

Met Lys Leu Ile Glu Pro Lys Lys Ala Phe Glu Ile Glu Leu Arg Ser

195 200 205

Lys Ala Gly Lys Ser Ser Gly Glu Lys Ile Gly Cys Gly Arg Ala Thr 210 215 220

Leu Arg Leu Arg Ser Lys Gly Pro Ala Thr Val Glu Glu Met Pro Ser 225 230 235 240

Glu Thr Lys Ala Lys Ala Ile Glu Lys Ile Asp Asp Val Leu Glu Leu 245 250 255

Tyr Met Gly Ile Arg Asp Ile Asp Leu Ala Thr Thr Met Phe Glu Ala 260 265 270

Gly Lys Asp Lys Val Asn Pro Asp Glu Phe Ala Val Ala Leu Asp Glu 275 280 285

Thr Leu Gly Asp Phe Ala Phe Pro Asp Glu Phe Val Phe Asp Val Trp 290 295 300

Gly Val Ile Gly Asp Ala Lys Arg Arg Gly Leu 305 310 315

<210> 149

<211> 486

<212> PRT

<213> Human

<400> 149

Met Pro Arg Pro Ala Pro Ala Arg Arg Leu Pro Gly Leu Leu Leu 1 5 10 15

Leu Trp Pro Leu Leu Leu Pro Ser Ala Ala Pro Asp Pro Val Ala 20 25 30

Arg Pro Gly Phe Arg Arg Leu Glu Thr Arg Gly Pro Gly Gly Ser Pro 35 40 45

Gly Arg Arg Pro Ser Pro Ala Ala Pro Asp Gly Ala Pro Ala Ser Gly 50 55 60

Thr Ser Glu Pro Gly Arg Ala Arg Gly Ala Gly Val Cys Lys Ser Arg 65 70 75 80

Pro Leu Asp Leu Val Phe Ile Ile Asp Ser Ser Arg Ser Val Arg Pro

90 95

Leu Glu Phe Thr Lys Val Lys Thr Phe Val Ser Arg Ile Ile Asp Thr 100 105 110

Leu Asp Ile Gly Pro Ala Asp Thr Arg Val Ala Val Val Asn Tyr Ala 115 120 125

Ser Thr Val Lys Ile Glu Phe Gln Leu Gln Ala Tyr Thr Asp Lys Gln 130 135 140

Ser Leu Lys Gln Ala Val Gly Arg Ile Thr Pro Leu Ser Thr Gly Thr 145 150 155 160

Met Ser Gly Leu Ala Ile Gln Thr Ala Met Asp Glu Ala Phe Thr Val 165 170 175

Glu Ala Gly Ala Arg Glu Pro Ser Ser Asn Ile Pro Lys Val Ala Ile 180 185 190

Ile Val Thr Asp Gly Arg Pro Gln Asp Gln Val Asn Glu Val Ala Ala 195 200 205

Arg Ala Gln Ala Ser Gly Ile Glu Leu Tyr Ala Val Gly Val Asp Arg 210 215 220

Ala Asp Met Ala Ser Leu Lys Met Met Ala Ser Glu Pro Leu Glu Glu 225 230 235 240

His Val Phe Tyr Val Glu Thr Tyr Gly Val Ile Glu Lys Leu Ser Ser 245 250 255

Arg Phe Gln Glu Thr Phe Cys Ala Leu Asp Pro Cys Val Leu Gly Thr 260 265 270

His Gln Cys Gln His Val Cys Ile Ser Asp Gly Glu Gly Lys His His 275 280 285

Cys Glu Cys Ser Gln Gly Tyr Thr Leu Asn Ala Asp Lys Lys Thr Cys 290 295 300

Ser Ala Leu Asp Arg Cys Ala Leu Asn Thr His Gly Cys Glu His Ile 305 310 315 320

Cys Val Asn Asp Arg Ser Gly Ser Tyr His Cys Glu Cys Tyr Glu Gly 325 330 335

Tyr Thr Leu Asn Glu Asp Arg Lys Thr Cys Ser Ala Gln Asp Lys Cys 340 345 350

Ala Leu Gly Thr His Gly Cys Gln His Ile Cys Val Asn Asp Arg Thr 355 360 365

Gly Ser His His Cys Glu Cys Tyr Glu Gly Tyr Thr Leu Asn Ala Asp 370 380

Lys Lys Thr Cys Ser Val Arg Asp Lys Cys Ala Leu Gly Ser His Gly 385 390 395 400

Cys Gln His Ile Cys Val Ser Asp Gly Ala Ala Ser Tyr His Cys Asp 405 410 415

Cys Tyr Pro Gly Tyr Thr Leu Asn Glu Asp Lys Lys Thr Cys Ser Ala 420 425 430

Thr Glu Glu Ala Arg Arg Leu Val Ser Thr Glu Asp Ala Cys Gly Cys 435 440 445

Glu Ala Thr Leu Ala Phe Gln Asp Lys Val Ser Ser Tyr Leu Gln Arg 450 455 460

Leu Asn Thr Lys Leu Asp Asp Ile Leu Glu Lys Leu Lys Ile Asn Glu 465 470 475 480

Tyr Gly Gln Ile His Arg 485

<210> 150

<211> 668

<212> PRT

<213> Human

<400> 150

Met Ala Ala Asn Met Tyr Arg Val Gly Asp Tyr Val Tyr Phe Glu Asn 1 5 10 15

Ser Ser Ser Asn Pro Tyr Leu Val Arg Arg Ile Glu Glu Leu Asn Lys 20 25 30

Thr Ala Asn Gly Asn Val Glu Ala Lys Val Val Cys Leu Phe Arg Arg 35 40 45

- Arg Asp Ile Ser Ser Ser Leu Asn Ser Leu Ala Asp Ser Asn Ala Arg 50 55 60
- Glu Phe Glu Glu Glu Ser Lys Gln Pro Gly Val Ser Glu Gln Gln Arg
 65 70 75 80
- His Gln Leu Lys His Arg Glu Leu Phe Leu Ser Arg Gln Phe Glu Ser 85 90 95
- Leu Pro Ala Thr His Ile Arg Gly Lys Cys Ser Val Thr Leu Leu Asn 100 105 110
- Glu Thr Asp Ile Leu Ser Gln Tyr Leu Glu Lys Glu Asp Cys Phe Phe 115 120 125
- Tyr Ser Leu Val Phe Asp Pro Val Gln Lys Thr Leu Leu Ala Asp Gln 130 135 140
- Gly Glu Ile Arg Val Gly Cys Lys Tyr Gln Ala Glu Ile Pro Asp Arg 145 150 155 160
- Leu Val Glu Gly Glu Ser Asp Asn Arg Asn Gln Gln Lys Met Glu Met 165 170 175
- Lys Val Trp Asp Pro Asp Asn Pro Leu Thr Asp Arg Gln Ile Asp Gln 180 185 190
- Phe Leu Val Val Ala Arg Ala Val Gly Thr Phe Ala Arg Ala Leu Asp 195 200 205
- Cys Ser Ser Ser Ile Arg Gln Pro Ser Leu His Met Ser Ala Ala 210 215 220
- Ala Ser Arg Asp Ile Thr Leu Phe His Ala Met Asp Thr Leu Gln Arg 225 230 235 240
- Asn Gly Tyr Asp Leu Ala Lys Ala Met Ser Thr Leu Val Pro Gln Gly 245 250 255
- Gly Pro Val Leu Cys Arg Asp Glu Met Glu Glu Trp Ser Ala Ser Glu 260 265 270

Ala Met Leu Phe Glu Glu Ala Leu Glu Lys Tyr Gly Lys Asp Phe Asn 280 Asp Ile Arg Gln Asp Phe Leu Pro Trp Lys Ser Leu Ala Ser Ile Val 295 Gln Phe Tyr Tyr Met Trp Lys Thr Thr Asp Arg Tyr Ile Gln Gln Lys 305 310 Arg Leu Lys Ala Ala Glu Ala Asp Ser Lys Leu Lys Gln Val Tyr Ile Pro Thr Tyr Thr Lys Pro Asn Pro Asn Gln Ile Ile Ser Val Gly Ser Lys Pro Gly Met Asn Gly Ala Gly Phe Gln Lys Gly Leu Thr Cys Glu 355 360 365 Ser Cys His Thr Thr Gln Ser Ala Gln Trp Tyr Ala Trp Gly Pro Pro 370 375 Asn Met Gln Cys Arg Leu Cys Ala Ser Cys Trp Ile Tyr Trp Lys Lys 390 395 400 Tyr Gly Gly Leu Lys Thr Pro Thr Gln Leu Glu Gly Ala Thr Arg Gly 405 Thr Thr Glu Pro His Ser Arg Gly His Leu Ser Arg Pro Glu Ala Gln 425 Ser Leu Ser Pro Tyr Thr Thr Ser Ala Asn Arg Ala Lys Leu Leu Ala 435 440 Lys Asn Arg Gln Thr Phe Leu Leu Gln Thr Thr Lys Leu Thr Arg Leu 450 Ala Arg Arg Met Cys Arg Asp Leu Leu Gln Pro Arg Arg Ala Ala Arg 470 475 480 Arg Pro Tyr Ala Pro Ile Asn Ala Asn Ala Ile Lys Ala Glu Cys Ser 485 490 495 Ile Arg Leu Pro Lys Ala Ala Lys Thr Pro Leu Lys Ile His Pro Leu 500 505 510

Val Arg Leu Pro Leu Ala Thr Ile Val Lys Asp Leu Val Ala Gln Ala 515 520 Pro Leu Lys Pro Lys Thr Pro Arg Gly Thr Lys Thr Pro Ile Asn Arg 535 Asn Gln Leu Ser Gln Asn Arg Gly Leu Gly Gly Ile Met Val Lys Arg 550 555 Ala Tyr Glu Thr Met Ala Gly Ala Gly Val Pro Phe Ser Ala Asn Gly 570 Arg Pro Leu Ala Ser Gly Ile Arg Ser Ser Ser Gln Pro Ala Ala Lys Arg Gln Lys Leu Asn Pro Ala Asp Ala Pro Asn Pro Val Val Phe Val 600 Ala Thr Lys Asp Thr Arg Ala Leu Arg Lys Ala Leu Thr His Leu Glu 610 615 620 Met Arg Arg Ala Ala Arg Arg Pro Asn Leu Pro Leu Lys Val Lys Pro 630 635 Thr Leu Ile Ala Val Arg Pro Pro Val Pro Leu Pro Ala Pro Ser His 645 650 Pro Ala Ser Thr Asn Glu Pro Ile Val Leu Glu Asp 660 665 <210> 151 <211> 5179 <212> PRT <213> Human <400> 151

Met Gly Leu Pro Leu Ala Arg Leu Ala Ala Val Cys Leu Ala Leu Ser 1 5 10 15

Leu Ala Gly Gly Ser Glu Leu Gln Thr Glu Gly Arg Thr Arg Tyr His 20 25 30

Gly Arg Asn Val Cys Ser Thr Trp Gly Asn Phe His Tyr Lys Thr Phe 35 40 45

Asp Gly Asp Val Phe Arg Phe Pro Gly Leu Cys Asp Tyr Asn Phe Ala 50 Ser Asp Cys Arg Gly Ser Tyr Lys Glu Phe Ala Val His Leu Lys Arg Gly Pro Gly Gln Ala Glu Ala Pro Ala Gly Val Glu Ser Ile Leu Leu Thr Ile Lys Asp Asp Thr Ile Tyr Leu Thr Arg His Leu Ala Val Leu 100 105 Asn Gly Ala Val Val Ser Thr Pro His Tyr Ser Pro Gly Leu Leu Ile 120 115 Glu Lys Ser Asp Ala Tyr Thr Lys Val Tyr Ser Arg Ala Gly Leu Thr 135 Leu Met Trp Asn Arg Glu Asp Ala Leu Met Leu Glu Leu Asp Thr Lys 150 155 Phe Arg Asn His Thr Cys Gly Leu Cys Gly Asp Tyr Asn Gly Leu Gln 165 170 Ser Tyr Ser Glu Phe Leu Ser Asp Gly Val Leu Phe Ser Pro Leu Glu 180 185 Phe Gly Asn Met Gln Lys Ile Asn Gln Pro Asp Val Val Cys Glu Asp 195 Pro Glu Glu Glu Val Ala Pro Ala Ser Cys Ser Glu His Arg Ala Glu 215 Cys Glu Arg Leu Leu Thr Ala Glu Ala Phe Ala Asp Cys Gln Asp Leu 230 235 Val Pro Leu Glu Pro Tyr Leu Arg Ala Cys Gln Gln Asp Arg Cys Arg 250 245 Cys Pro Gly Gly Asp Thr Cys Val Cys Ser Thr Val Ala Glu Phe Ser 260 265 270 Arg Gln Cys Ser His Ala Gly Gly Arg Pro Gly Asn Trp Arg Thr Ala

275 280 285

Thr Leu Cys Pro Lys Thr Cys Pro Gly Asn Leu Val Tyr Leu Glu Ser 290 295 300

Gly Ser Pro Cys Met Asp Thr Cys Ser His Leu Glu Val Ser Ser Leu 305 310 315 320

Cys Glu Glu His Arg Met Asp Gly Cys Phe Cys Pro Glu Gly Thr Val 325 330 335

Tyr Asp Asp Ile Gly Asp Ser Gly Cys Val Pro Val Ser Gln Cys His 340 345 350

Cys Arg Leu His Gly His Leu Tyr Thr Pro Gly Gln Glu Ile Thr Asn 355 360 365

Asp Cys Glu Gln Cys Val Cys Asn Ala Gly Arg Trp Val Cys Lys Asp 370 380

Leu Pro Cys Pro Gly Thr Cys Ala Leu Glu Gly Gly Ser His Ile Thr 385 390 395 400

Thr Phe Asp Gly Lys Thr Tyr Thr Phe His Gly Asp Cys Tyr Tyr Val 405 410 415

Leu Ala Lys Gly Asp His Asn Asp Ser Tyr Ala Leu Leu Gly Glu Leu 420 425 430

Ala Pro Cys Gly Ser Thr Asp Lys Gln Thr Cys Leu Lys Thr Val Val 435 440 445

Leu Leu Ala Asp Lys Lys Lys Asn Ala Val Val Phe Lys Ser Asp Gly 450 455 460

Ser Val Leu Leu Asn Gln Leu Gln Val Asn Leu Pro His Val Thr Ala 465 470 475 480

Ser Phe Ser Val Phe Arg Pro Ser Ser Tyr His Ile Met Val Ser Met 485 490 495

Ala Ile Gly Val Arg Leu Gln Val Gln Leu Ala Pro Val Met Gln Leu 500 505 510

and hant I or that and same ...

Phe Val Thr Leu Asp Gln Ala Ser Gln Gly Gln Val Gln Gly Leu Cys 515 520 525

Gly Asn Phe Asn Gly Leu Glu Gly Asp Asp Phe Lys Thr Ala Ser Gly 530 535 540

Leu Val Glu Ala Thr Gly Ala Gly Phe Ala Asn Thr Trp Lys Ala Gln 545 550 555 560

Ser Thr Cys His Asp Lys Leu Asp Trp Leu Asp Asp Pro Cys Ser Leu 565 570 575

Asn Ile Glu Ser Ala Asn Tyr Ala Glu His Trp Cys Ser Leu Leu Lys 580 585 590

Lys Thr Glu Thr Pro Phe Gly Arg Cys His Ser Ala Val Asp Pro Ala 595 600 605

Glu Tyr Tyr Lys Arg Cys Lys Tyr Asp Thr Cys Asn Cys Gln Asn Asn 610 615 620

Glu Asp Cys Leu Cys Ala Ala Leu Ser Ser Tyr Ala Arg Ala Cys Thr 625 630 635 640

Ala Lys Gly Val Met Leu Trp Gly Trp Arg Glu His Val Cys Asn Lys 645 650 655

Asp Val Gly Ser Cys Pro Asn Ser Gln Val Phe Leu Tyr Asn Leu Thr 660 665 670

Thr Cys Gln Gln Thr Cys Arg Ser Leu Ser Glu Ala Asp Ser His Cys 675 680 685

Leu Glu Gly Phe Ala Pro Val Asp Gly Cys Gly Cys Pro Asp His Thr 690 695 700

Phe Leu Asp Glu Lys Gly Arg Cys Val Pro Leu Ala Lys Cys Ser Cys 705 710 715 720

Tyr His Arg Gly Leu Tyr Leu Glu Ala Gly Asp Val Val Arg Gln 725 730 735

Glu Glu Arg Cys Val Cys Arg Asp Gly Arg Leu His Cys Arg Gln Ile 740 745 750

half have the first shall shall make in the state stone more more some

Arg Leu Ile Gly Gln Ser Cys Thr Ala Pro Lys Ile His Met Asp Cys 755 760 765

Ser Asn Leu Thr Ala Leu Ala Thr Ser Lys Pro Arg Ala Leu Ser Cys 770 780

Gln Thr Leu Ala Ala Gly Tyr Tyr His Thr Glu Cys Val Ser Gly Cys 785 790 795 800

Val Cys Pro Asp Gly Leu Met Asp Asp Gly Arg Gly Gly Cys Val Val 805 810 815

Glu Lys Glu Cys Pro Cys Val His Asn Asn Asp Leu Tyr Ser Ser Gly 820 825 830

Ala Lys Ile Lys Val Asp Cys Asn Thr Cys Thr Cys Lys Arg Gly Arg 835 840 845

Trp Val Cys Thr Gln Ala Val Cys His Gly Thr Cys Ser Ile Tyr Gly 850 855 860

Ser Gly His Tyr Ile Thr Phe Asp Gly Lys Tyr Tyr Asp Phe Asp Gly 865 870 875 880

His Cys Ser Tyr Val Ala Val Gln Asp Tyr Cys Gly Gln Asn Ser Ser 885 890 895

Leu Gly Ser Phe Ser Ile Ile Thr Glu Asn Val Pro Cys Gly Thr Thr 900 905 910

Gly Val Thr Cys Ser Lys Ala Ile Lys Ile Phe Met Gly Arg Thr Glu 915 920 925

Leu Lys Leu Glu Asp Lys His Arg Val Val Ile Gln Arg Asp Glu Gly 930 935 940

His His Val Ala Tyr Thr Thr Arg Glu Val Gly Gln Tyr Leu Val Val 945 950 955 960

Glu Ser Ser Thr Gly Ile Ile Val Ile Trp Asp Lys Arg Thr Thr Val 965 970 975

Phe Ile Lys Leu Ala Pro Ser Tyr Lys Gly Thr Val Cys Gly Leu Cys 980 985 990

The land and the said both to the first that that the

Gly Asn Phe Asp His Arg Ser Asn Asn Asp Phe Thr Thr Arg Asp His 995 1000 1005

Met Val Val Ser Ser Glu Leu Asp Phe Gly Asn Ser Trp Lys Glu 1010 1015 1020

Ala Pro Thr Cys Pro Asp Val Ser Thr Asn Pro Glu Pro Cys Ser 1025 1030 1035

Leu Asn Pro His Arg Arg Ser Trp Ala Glu Lys Gln Cys Ser Ile 1040 1045 1050

Leu Lys Ser Ser Val Phe Ser Ile Cys His Ser Lys Val Asp Pro 1055 1060 1065

Lys Pro Phe Tyr Glu Ala Cys Val His Asp Ser Cys Ser Cys Asp 1070 1075 1080

Thr Gly Gly Asp Cys Glu Cys Phe Cys Ser Ala Val Ala Ser Tyr 1085 1090 1095

Ala Gln Glu Cys Thr Lys Glu Gly Ala Cys Val Phe Trp Arg Thr 1100 1105 1110

Pro Asp Leu Cys Pro Ile Phe Cys Asp Tyr Tyr Asn Pro Pro His 1115 1120 1125

Glu Cys Glu Trp His Tyr Glu Pro Cys Gly Asn Arg Ser Phe Glu 1130 1135 1140

Thr Cys Arg Thr Ile Asn Gly Ile His Ser Asn Ile Ser Val Ser 1145 1150 1155

Tyr Leu Glu Gly Cys Tyr Pro Arg Cys Pro Lys Asp Arg Pro Ile 1160 1165 1170

Tyr Glu Glu Asp Leu Lys Lys Cys Val Thr Ala Asp Lys Cys Gly 1175 1180 1185

Cys Tyr Val Glu Asp Thr His Tyr Pro Pro Gly Ala Ser Val Pro 1190 1195 1200

Thr Glu Glu Thr Cys Lys Ser Cys Val Cys Thr Asn Ser Ser Gln

port hat I or had tank and a comment of

$\ _{m_{\mathbf{h}}} \ \ ^{\mathrm{out}}$	H or And	i tranti ilmi	H 29 6"											
	1205					1210					1215			
Val	Val 1220		Arg	Pro	Glu	Glu 1225	Gly	Lys	Ile	Leu	Asn 1230		Thr	Gln
Asp	Gly 1235		Phe	Cys	Tyr	Trp 1240		Ile	Cys	Gly	Pro 1245	Asn	Gly	Thr
Val	Glu 1250		His	Phe	Asn	Ile 1255		Ser	Ile	Thr	Thr 1260		Pro	Ser
Thr	Leu 1265	Thr	Thr	Phe	Thr	Thr 1270		Thr	Leu	Pro	Thr 1275	Thr	Pro	Thr
Ser	Phe 1280		Thr	Thr	Thr	Thr 1285	Thr	Thr	Thr	Pro	Thr 1290	Ser	Ser	Thr
Val	Leu 1295	Ser	Thr	Thr	Pro	Lys 1300	Leu	Cys	Cys	Leu	Trp 1305	Ser	Asp	Trp
Ile	Asn 1310	Glu	Asp	His	Pro	Ser 1315	Ser	Gly	Ser		Asp 1320	Gly	Asp	Arg
Glu	Pro 1325	Phe	Asp	Gly	Val	Cys 1330	Gly	Ala	Pro	Glu	Asp 1335	Ile	Glu	Cys
Arg	Ser 1340	Val	Lys	Asp	Pro	His 1345	Leu	Ser	Leu	Glu	Gln 1350	His	Gly	Gln
						Ser 1360							Asn	Glu
Asp	Gln 1370	Phe	Gly	Asn	Gly	Pro 1375	Phe	Gly	Leu	Cys	Tyr 1380	Asp	Tyr	Lys
Ile	Arg 1385	Val	Asn	Cys	Cys	Trp 1390	Pro	Met	Asp	Lys	Cys 1395	Ile	Thr	Thr
Pro	Ser 1400	Pro	Pro	Thr	Thr	Thr 1405	Pro	Ser	Pro	Pro	Pro 1410	Thr	Thr	Thr
Thr	Thr 1415	Leu	Pro	Pro	Thr	Thr 1420	Thr	Pro	Ser	Pro	Pro 1425	Thr	Thr	Thr

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Thr	Thr 1430	Thr	Pro	Pro	Pro	Thr 1435	Thr	Thr	Prc	Ser	Pro 1440		> Il∈	e Thr
Thr	Thr 1445	Thr	Thr	Pro	Leu	Pro 1450		Thr	Thr	Pro	Ser 1455		Pro) Ile
Ser	Thr 1460	Thr	Thr	Thr	Pro	Pro 1465		Thr	Thr	Thr	Pro 1470		Pro	Pro
Thr	Thr 1475	Thr	Pro	Ser	Pro	Pro 1480		Thr	Thr	Pro	Ser 1485		Pro	Thr
Thr	Thr 1490	Thr	Thr	Thr	Pro	Pro 1495	Pro	Thr	Thr	Thr	Pro 1500		Pro	Pro
Met	Thr 1505	Thr	Pro	Ile	Thr	Pro 1510	Pro	Ala	Ser	Thr	Thr 1515	Thr	Leu	Pro
Pro	Thr 1520	Thr	Thr	Pro	Ser	Pro 1525	Pro	Thr	Thr	Thr	Thr 1530	Thr	Thr	Pro
Pro	Pro 1535	Thr	Thr	Thr	Pro	Ser 1540	Pro	Pro	Thr	Thr	Thr 1545	Pro	Ile	Thr
Pro	Pro 1550	Thr	Ser	Thr	Thr	Thr 1555	Leu	Pro	Pro	Thr	Thr 1560	Thr	Pro	Ser
Pro	Pro 1565	Pro	Thr	Thr	Thr	Thr 1570	Thr	Pro	Pro	Pro	Thr 1575	Thr	Thr	Pro
Ser	Pro 1580	Pro	Thr	Thr	Thr	Thr 1585	Pro	Ser	Pro	Pro	Thr 1590	Ile	Thr	Thr
Thr	Thr 1595	Pro	Pro	Pro	Thr	Thr 1600	Thr	Pro	Ser	Pro	Pro 1605	Thr	Thr	Thr
Thr	Thr 1610	Thr	Pro	Pro		Thr 1615	Thr	Thr	Pro	Ser	Pro 1620	Pro	Thr	Thr
Thr	Pro 1625	Ile	Thr	Pro		Thr 1630	Ser	Thr	Thr		Leu 1635	Pro	Pro	Thr
Thr	Thr 1640	Pro	Ser	Pro :		Pro 1645	Thr	Thr	Thr		Thr 1650	Pro	Pro	Pro

Thr	Thr 1655	Thr	Pro	Ser	Pro	Pro 1660	Thr	Thr	Thr	Thr	Pro 1665	Ser	Pro	Pro
Ile	Thr 1670	Thr	Thr	Thr	Thr	Pro 1675	Pro	Pro	Thr	Thr	Thr 1680	Pro	Ser	Ser
Pro	Ile 1685		Thr	Thr		Ser 1690		Pro	Thr	Thr	Thr 1695	Met	Thr	Thr
Pro	Ser 1700		Thr	Thr	Thr	Pro 1705		Ser	Pro	Ile	Thr 1710	Thr	Thr	Thr
Thr	Pro 1715		Ser	Thr	Thr	Thr 1720		Ser	Pro	Pro	Pro 1725		Thr	Met
Thr	Thr 1730	Pro	Ser	Pro		Thr 1735		Pro	Ser	Pro	Pro 1740	Thr	Thr	Thr
Met	Thr 1745		Leu	Pro	Pro	Thr 1750		Thr	Ser	Ser	Pro 1755		Thr	Thr
Thr	Pro 1760		Pro	Pro	Ser	Ile 1765		Pro	Pro	Thr	Phe 1770	Ser	Pro	Phe
Ser	Thr 1775		Thr	Pro	Thr	Thr 1780		Cys	Val	Pro	Leu 1785		Asn	Trp
Thr	Gly 1790		Leu	Asp	Ser	Gly 1795	Lys	Pro	Asn	Phe	His 1800	Lys	Pro	Gly
Gly	Asp 1805			Leu		Gly 1810		Val	Cys	Gly	Pro 1815	Gly	Trp	Ala
Ala	Asn 1820		Ser	Cys	Arg	Ala 1825		Met	Tyr	Pro	Asp 1830		Pro	Ile
Gly	Gln 1835		. Gly	Gln	Thr	Val 1840		Cys	Asp	Val	Ser 1845		Gly	Leu
Ile	Cys 1850	_	Asn	ı Glu	Asp	Gln 1855		Pro	Gly	· Gly	Val 1860		Pro	Met
Ala	. Phe 1865		. Leu	ı Asn	Tyr	Glu 1870		Asn	. Val	Gln	Cys 1875		Glu	Cys

Val	Thr 1880	Gln	Pro	Thr	Thr	Met 1885	Thr	Thr	Thr	Thr	Thr 1890	Glu	Asn	Pro
Thr	Pro 1895	Pro	Thr	Thr	Thr	Pro 1900	Ile	Thr	Thr	Thr	Thr 1905	Thr	Val	Thr
Pro	Thr 1910		Thr	Pro	Thr	Gly 1915	Thr	Gln	Thr	Pro	Thr 1920	Thr	Thr	Pro
Ile	Thr 1925	Thr	Thr	Thr	Thr	Val 1930	Thr	Pro	Thr	Pro	Thr 1935	Pro	Thr	Gly
Thr	Gln 1940		Pro	Thr	Thr	Thr 1945	Pro	Ile	Thr	Thr	Thr 1950	Thr	Thr	Val
Thr	Pro 1955		Pro	Thr	Pro	Thr 1960		Thr	Gln	Thr	Pro 1965		Thr	Thr
Pro	Ile 1970		Thr	Thr	Thr	Thr 1975		Thr	Pro	Thr	Pro 1980	Thr	Pro	Thr
Gly	Thr 1985		Thr	Pro	Thr	Thr 1990		Pro	Ile		Thr 1995		Thr	Thr
Val	Thr 2000		Thr	Pro	Thr	Pro 2005		Gly	Thr	Gln	Thr 2010	Pro	Thr	Thr
Thr	Pro 2015		Thr	Thr	Thr	Thr 2020		Val	Thr		Thr 2025		Thr	Pro
Thr	Gly 2030	Thr	Gln	Thr	Pro	Thr 2035	Thr	Thr	Pro	Ile	Thr 2040	Thr	Thr	Thr
Thr	Val 2045		Pro	Thr	Pro	Thr 2050	Pro	Thr	Gly	Thr	Gln 2055	Thr	Pro	Thr
Thr	Thr 2060		Ile	Thr	Thr	Thr 2065		Thr	Val	Thr	Pro 2070	Thr	Pro	Thr
Pro	Thr 2075		Thr	Gln	Thr	Pro 2080		Thr	Thr	Pro	Ile 2085	Thr	Thr	Thr
Thr	Thr	Val	Thr	Pro	Thr	Pro	Thr	Pro	Thr	Gly	Thr	Gln	Thr	Pro

	2090					2095					2100			
Thr	Thr 2105	Thr	Pro	Ile	Thr	Thr 2110		Thr	Thr	Val	Thr 2115	Pro	Thr	Pro
Thr	Pro 2120	Thr	Gly	Thr	Gln	Thr 2125	Pro	Thr	Thr	Thr	Pro 2130	Ile	Thr	Thr
Thr	Thr 2135	Thr	Val	Thr	Pro	Thr 2140	Pro	Thr	Pro	Thr	Gly 2145	Thr	Gln	Thr
Pro	Thr 2150	Thr	Thr	Pro	Ile	Thr 2155	Thr	Thr	Thr	Thr	Val 2160	Thr	Pro	Thr
Pro	Thr 2165	Pro	Thr	Gly		Gln 2170	Thr	Pro	Thr	Thr	Thr 2175	Pro	Ile	Thr
Thr	Thr 2180	Thr	Thr	Val	Thr	Pro 2185	Thr	Pro	Thr	Pro	Thr 2190	Gly	Thr	Gln
Thr	Pro 2195	Thr	Thr	Thr		Ile 2200	Thr	Thr	Thr	Thr	Thr 2205	Val	Thr	Pro
Thr	Pro 2210	Thr	Pro	Thr		Thr 2215	Gln	Thr	Pro	Thr	Thr 2220	Thr	Pro	Ile
Thr	Thr 2225	Thr	Thr	Thr		Thr 2230	Pro	Thr	Pro	Thr	Pro 2235	Thr	Gly	Thr
Gln	Thr 2240	Pro	Thr	Thr	Thr	Pro 2245	Ile	Thr	Thr	Thr	Thr 2250	Thr	Val	Thr
Pro	Thr 2255	Pro	Thr	Pro	Thr	Gly 2260	Thr	Gln	Thr	Pro	Thr 2265	Thr	Thr	Pro
Ile	Thr 2270	Thr	Thr	Thr	Thr	Val 2275	Thr	Pro	Thr	Pro	Thr 2280	Pro	Thr	Gly
Thr	Gln 2285	Thr	Pro	Thr	Thr	Thr 2290	Pro	Ile	Thr	Thr	Thr 2295	Thr	Thr	Val
Thr	Pro 2300	Thr	Pro	Thr	Pro	Thr 2305	Gly	Thr	Gln	Thr	Pro 2310	Thr	Thr	Thr

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Pro	Ile 2315		Thr	Thr		Thr 2320	Val	Thr	Pro	Thr	Pro 2325	Thr	Pro	Thr
Gly	Thr 2330		Thr	Pro	Thr	Thr 2335	Thr	Pro	Ile	Thr	Thr 2340	Thr	Thr	Thr
Val	Thr 2345		Thr	Pro		Pro 2350		Gly	Thr	Gln	Thr 2355	Pro	Thr	Thr
Thr	Pro 2360	Ile	Thr			Thr 2365		Val	Thr		Thr 2370		Thr	Pro
Thr	Gly 2375		Gln	Thr		Thr 2380		Thr		Ile	Thr 2385	Thr	Thr	Thr
Thr	Val 2390		Pro	Thr		Thr 2395		Thr	Gly	Thr	Gln 2400	Thr	Pro	Thr
Thr	Thr 2405		Ile	Thr	Thr	Thr 2410		Thr	Val	Thr	Pro 2415	Thr	Pro	Thr
Pro	Thr 2420		Thr	Gln		Pro 2425		Thr	Thr	Pro	Ile 2430	Thr	Thr	Thr
Thr	Thr 2435		Thr	Pro	Thr	Pro 2440		Pro	Thr	Gly	Thr 2445		Thr	Pro
Thr	Thr 2450		Pro	Ile		Thr 2455		Thr	Thr	Val	Thr 2460		Thr	Pro
	Pro 2465		Gly	Thr	Gln	Thr	Pro	Thr	Thr	Thr	Pro 2475	Ile	Thr	Thr
Thr	Thr 2480		Val	Thr	Pro	Thr 2485		Thr	Pro	Thr	Gly 2490	Thr	Gl'n	Thr
Pro	Thr 2495		Thr	Pro	Ile	Thr 2500		Thr	Thr	Thr	Val 2505	Thr	Pro	Thr
Pro	Thr 2510		Thr	: Gly	Thr	Gln 2515	Thr	Pro	Thr	Thr	Thr 2520	Pro	Ile	Thr
Thr	Thr 2525		Thr	: Val	. Thr	Pro 2530		: Pro	Thr	Pro	Thr 2535		Thr	Gln

Thr	Pro 2540	Thr	Thr	Thr		Ile 2545	Thr	Thr	Thr	Thr	Thr 2550	Val	Thr	Pro
Thr	Pro 2555	Thr	Pro	Thr	Gly	Thr 2560	Gln	Thr	Pro	Thr	Thr 2565	Thr	Pro	Ile
Thr	Thr 2570	Thr	Thr	Thr		Thr 2575	Pro	Thr	Pro		Pro 2580	Thr	Gly	Thr
Gln	Thr 2585	Pro	Thr	Thr		Pro 2590	Ile	Thr	Thr	Thr	Thr 2595	Thr	Val	Thr
Pro	Thr 2600		Thr	Pro		Gly 2605	Thr	Gln	Thr		Thr 2610	Thr	Thr	Pro
Ile	Thr 2615		Thr	Thr		Val 2620		Pro	Thr		Thr 2625	Pro	Thr	Gly
Thr	Gln 2630		Pro			Thr 2635		Ile	Thr	Thr	Thr 2640	Thr	Thr	Val
Thr	Pro 2645		Pro	Thr		Thr 2650		Thr	Gln	Thr	Pro 2655	Thr	Thr	Thr
Pro	Ile 2660		Thr			Thr 2665		Thr			Pro 2670		Pro	Thr
Gly	Thr 2675		Thr	Pro		Thr 2680		Pro	Ile	Thr	Thr 2685		Thr	Thr
Val						Pro 2695							Thr	Thr
Thr	Pro 2705	Ile	Thr	Thr	Thr	Thr 2710	Thr	Val	Thr	Pro	Thr 2715	Pro	Thr	Pro
Thr	Gly 2720		Gln	Thr	Pro	Thr 2725	Thr	Thr	Pro	Ile	Thr 2730	Thr	Thr	Thr
Thr	Val 2735		Pro	Thr	Pro	Thr 2740	Pro	Thr	Gly	Thr	Gln 2745	Thr	Pro	Thr
Thr	Thr 2750		Ile	Thr	Thr	Thr 2755		Thr	Val	Thr	Pro 2760		Pro	Thr

Pro	Thr 2765	Gly	Thr	Gln		Pro 2770		Thr	Thr		Ile 2775		Thr	Thr
Thr	Thr 2780		Thr	Pro	Thr	Pro 2785		Pro	Thr	Gly	Thr 2790		Thr	Pro
Thr	Thr 2795	Thr	Pro	Ile		Thr 2800		Thr	Thr		Thr 2805	Pro	Thr	Pro
Thr	Pro 2810		Gly	Thr		Thr 2815		Thr	Thr		Pro 2820		Thr	Thr
Thr	Thr 2825		Val	Thr		Thr 2830		Thr	Pro	Thr	Gly 2835		Gln	Thr
Pro	Thr 2840		Thr	Pro		Thr 2845		Thr	Thr	Thr	Val 2850		Pro	
Pro	Thr 2855	Pro	Thr	Gly	Thr	Gln 2860	Thr	Pro	Thr	Thr	Thr 2865	Pro	Ile	Thr
Thr	Thr 2870	Thr	Thr	Val		Pro 2875	Thr	Pro	Thr	Pro	Thr 2880	Gly	Thr	Gln
Thr	Pro 2885	Thr	Thr	Thr	Pro	Ile 2890	Thr	Thr	Thr	Thr	Thr 2895	Val	Thr	Pro
Thr	Pro 2900	Thr	Pro	Thr		Thr 2905	Gln	Thr	Pro	Thr	Thr 2910	Thr	Pro	Ile
Thr	Thr 2915					Thr 2920							Gly	Thr
Gln	Thr 2930	Pro	Thr	Thr	Thr	Pro 2935	Ile	Thr	Thr	Thr	Thr 2940	Thr	Val	Thr
Pro	Thr 2945	Pro	Thr	Pro	Thr	Gly 2950		Gln	Thr	Pro	Thr 2955	Thr	Thr	Pro
Ile	Thr 2960	Thr	Thr	Thr	Thr	Val 2965	Thr	Pro	Thr	Pro	Thr 2970	Pro	Thr	Gly
Thr	Gln	Thr	Pro	Thr	Thr	Thr	Pro	Ile	Thr	Thr	Thr	Thr	Thr	Val

	2975					2980					2985			
Thr	Pro 2990		Pro	Thr	Pro	Thr 2995		Thr	Gln	Thr	Pro 3000		Thr	Thr
Pro	Ile 3005	Thr	Thr	Thr	Thr	Thr 3010	Val	Thr	Pro	Thr	Pro 3015	Thr	Pro	Thr
Gly	Thr 3020		Thr	Pro	Thr	Thr 3025	Thr	Pro	Ile	Thr	Thr 3030		Thr	Thr
Val	Thr 3035		Thr	Pro		Pro 3040		Gly	Thr	Gln	Thr 3045		Thr	Thr
Thr	Pro 3050	Ile				Thr 3055	Thr	Val	Thr	Pro	Thr 3060	Pro	Thr	Pro
Thr	Gly 3065	Thr	Gln	Thr		Thr 3070		Thr	Pro	Ile	Thr 3075	Thr	Thr	Thr
Thr	Val 3080	Thr	Pro	Thr		Thr 3085		Thr	Gly	Thr	Gln 3090		Pro	Thr
Thr	Thr 3095	Pro	Ile	Thr		Thr 3100	Thr	Thr	Val	Thr	Pro 3105	Thr	Pro	Thr
Pro	Thr 3110	Gly	Thr	Gln		Pro 3115	Thr	Thr	Thr	Pro	Ile 3120	Thr	Thr	Thr
Thr	Thr		Thr			Pro		Pro	Thr		Thr		Thr	Pro

Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Pro Ile Thr Thr 3155 3160 3165

Thr Thr Thr Pro Ile Thr Thr Thr Thr Val Thr Pro Thr Pro

3125 3130 3135

3140 3145 3150

Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr 3170 3175 3180

Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr 3185 3190 3195

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Pro	Thr 3200	Pro	Thr	Gly	Thr	Gln 3205	Thr	Pro	Thr	Thr	Thr 3210	Pro	Ile	Thr
Thr	Thr 3215		Thr	Val	Thr	Pro 3220	Thr	Pro	Thr	Pro	Thr 3225	Gly	Thr	Gln
Thr	Pro 3230	Thr	Thr	Thr	Pro	Ile 3235	Thr	Thr	Thr	Thr	Thr 3240	Val	Thr	Pro
Thr	Pro 3245		Pro	Thr	Gly	Thr 3250	Gln	Thr	Pro	Thr	Thr 3255	Thr	Pro	Ile
Thr	Thr 3260		Thr			Thr 3265					Pro 3270	Thr	Gly	Thr
Gln	Thr 3275		Thr	Thr		Pro 3280		Thr	Thr	Thr	Thr 3285		Val	Thr
Pro	Thr 3290		Thr	Pro	Thr	Gly 3295					Thr 3300	Thr	Thr	Pro
Ile	Thr 3305		Thr	Thr		Val 3310		Pro	Thr	Pro	Thr 3315	Pro	Thr	Gly
Thr	Gln 3320		Pro	Thr	Thr	Thr 3325		Ile	Thr	Thr	Thr 3330	Thr	Thr	Val
Thr	Pro 3335		Pro	Thr	Pro	Thr 3340	Gly	Thr	Gln	Thr	Pro 3345	Thr	Thr	Thr
	Ile 3350			Thr	Thr	Thr 3355	Val	Thr	Pro	Thr	Pro 3360	Thr	Pro	Thr
Gly	Thr 3365		Thr	Pro	Thr	Thr 3370	Thr	Pro	Ile	Thr	Thr 3375	Thr	Thr	Thr
Val	Thr 3380		Thr	Pro	Thr	Pro 3385		Gly	Thr	Gln	Thr 3390	Pro	Thr	Thr
Thr	Pro 3395		Thr	Thr	Thr	Thr 3400		· Val	. Thr	Pro	Thr 3405		Thr	Pro
Thr	Gly 3410		Glr	ı Thr	: Pro	Thr 3415		Thr	Pro	. Ile	Thr 3420	Thr	Thr	Thr

Thr	Val 3425	Thr	Pro	Thr	Pro	Thr 3430		Thr	Gly	Thr	Gln 3435	Thr	Pro	Thr
Thr	Thr 3440	Pro	Ile	Thr	Thr	Thr 3445	Thr	Thr	Val	Thr	Pro 3450	Thr	Pro	Thr
Pro	Thr 3455	Gly	Thr	Gln	Thr	Pro 3460	Thr	Thr	Thr	Pro	Ile 3465	Thr	Thr	Thr
Thr	Thr 3470	Val	Thr	Pro	Thr	Pro 3475	Thr	Pro	Thr	Gly	Thr 3480		Thr	Pro
Thr	Thr 3485	Thr	Pro	Ile	Thr	Thr 3490	Thr	Thr	Thr	Val	Thr 3495	Pro	Thr	Pro
Thr	Pro 3500	Thr	Gly	Thr	Gln	Thr 3505	Pro	Thr	Thr	Thr	Pro 3510		Thr	Thr
Thr	Thr 3515		Val	Thr	Pro	Thr 3520		Thr	Pro		Gly 3525		Gln	Thr
Pro	Thr 3530	Thr	Thr	Pro	Ile	Thr 3535		Thr	Thr		Val 3540		Pro	Thr
Pro	Thr 3545	Pro	Thr	Gly	Thr	Gln 3550	Thr	Pro	Thr	Thr	Thr 3555	Pro	Ile	Thr
Thr	Thr 3560	Thr	Thr	Val	Thr	Pro 3565	Thr	Pro	Thr		Thr 3570	Gly	Thr	Gln
Thr	Pro 3575					Ile 3580							Thr	Pro
Thr	Pro 3590	Thr	Pro	Thr	Gly	Thr 3595	Gln	Thr	Pro	Thr	Thr 3600	Thr	Pro	Ile
Thr	Thr 3605	Thr	Thr	Thr	Val	Thr 3610	Pro	Thr	Pro	Thr	Pro 3615	Thr	Gly	Thr
Gln	Thr 3620	Pro	Thr	Thr	Thr	Pro 3625	Ile	Thr	Thr	Thr	Thr 3630	Thr	Val	Thr
Pro	Thr 3635	Pro	Thr	Pro	Thr	Gly 3640	Thr	Gln	Thr	Pro	Thr 3645	Thr	Thr	Pro

Ile	Thr 3650		Thr	Thr	Thr	Val 3655		Pro	Thr	Pro	Thr 3660		Thr	Gly
Thr	Gln 3665		Pro	Thr	Thr	Thr 3670		Ile	Thr	Thr	Thr 3675		Thr	Val
Thr	Pro 3680		Pro	Thr	Pro	Thr 3685		Thr	Gln	Thr	Pro 3690		Thr	Thr
Pro	Ile 3695		Thr	Thr		Thr 3700		Thr	Pro	Thr	Pro 3705		Pro	Thr
Gly	Thr 3710		Thr	Pro	Thr	Thr 3715		Pro	Ile	Thr	Thr 3720	Thr	Thr	Thr
Val	Thr 3725	Pro	Thr	Pro	Thr	Pro 3730	Thr	Gly	Thr	Gln	Thr 3735	Pro	Thr	Thr
Thr	Pro 3740	Ile	Thr	Thr	Thr	Thr 3745	Thr	Val	Thr	Pro	Thr 3750	Pro	Thr	Pro
Thr	Gly 3755	Thr	Gln	Thr	Pro	Thr 3760	Thr	Thr	Pro	Ile	Thr 3765	Thr	Thr	Thr
Thr	Val 3770	Thr	Pro	Thr	Pro	Thr 3775	Pro	Thr	Gly	Thr	Gln 3780	Thr	Pro	Thr
Thr	Thr 3785	Pro	Ile	Thr	Thr	Thr 3790	Thr	Thr	Val	Thr	Pro 3795	Thr	Pro	Thr
Pro	Thr 3800	Gly	Thr	Gln	Thr	Pro 3805	Thr	Thr	Thr		Ile 3810		Thr	Thr
Thr	Thr 3815	Val	Thr	Pro	Thr	Pro 3820	Thr	Pro	Thr	Gly	Thr 3825	Gln	Thr	Pro
Thr	Thr 3830	Thr	Pro	Ile	Thr	Thr 3835	Thr	Thr	Thr	Val	Thr 3840	Pro	Thr	Pro
Thr	Pro 3845	Thr	Gly	Thr	Gln	Thr 3850	Pro	Thr	Thr	Thr	Pro 3855	Ile	Thr	Thr
Thr	Thr	Thr	Val	Thr	Pro	Thr	Pro	Thr	Pro	Thr	Gly	Thr	Gln	Thr

	3860					3865					3870			
	Thr 3875	Thr	Thr	Pro		Thr 3880	Thr	Thr	Thr		Val 3885	Thr	Pro	Thr
	Thr 3890	Pro	Thr	Gly	Thr	Gln 3895	Thr	Pro	Thr	Thr	Thr 3900	Pro	Ile	Thr
	Thr 3905	Thr	Thr	Val	Thr	Pro 3910	Thr	Pro	Thr	Pro	Thr 3915	Gly	Thr	Gln
	Pro 3920	Thr	Thr	Thr	Pro	Ile 3925	Thr	Thr	Thr	Thr	Thr 3930	Val	Thr	Pro
Thr	Pro 3935		Pro	Thr	Gly	Thr 3940	Gln	Thr	Pro	Thr	Thr 3945	Thr	Pro	Ile
Thr	Thr 3950		Thr	Thr	Val	Thr 3955	Pro	Thr	Pro	Thr	Pro 3960	Thr	Gly	Thr
Gln	Thr 3965		Thr	Thr	Thr	Pro 3970	Ile	Thr	Thr	Thr	Thr 3975	Thr	Val	Thr
Pro	Thr 3980		Thr	Pro	Thr	Gly 3985	Thr	Gln	Thr	Pro	Thr 3990	Thr	Thr	Pro
Ile	Thr 3995		Thr	Thr		Val 4000		Pro	Thr	Pro	Thr 4005	Pro	Thr	Gly
Thr	Gln 4010		Pro	Thr	Thr	Thr 4015		Ile	Thr	Thr	Thr 4020	Thr	Thr	Val
Thr	Pro 4025		· Prc	Thr	Pro	Thr 4030		Thr	Gln	Thr	Pro 4035	Thr	Thr	Thr
Pro	Ile 4040		Thr	Thr	Thr	Thr 4045		Thr	Pro	Thr	Pro 4050	Thr	Pro	Thr
Gly	Thr 4055		n Thi	r Pro	Thr	Thr 4060		Pro	. Ile	. Thr	Thr 4065	Thr	Thr	Thr
Val	Thr 4070) Thi	r Pro	Thi	Pro 4075		: Gly	Thr	Gln	1 Thr 4080	Pro	Thi	Thr

Thr	Pro 408	I10 5	e Th	r Th	r Th	r Thr 4090	Thi	r Val	l Thi	r Pro	Thr 409		o Th	r Pro
Thr	Gly 4100	Th:	r Gli	n Th:	r Pro	o Thr 4105	Thr	Thr	Pro) Ile	Thr 4110		: Th:	r Thr
Thr	Val 4115	Thi	r Pro	o Thi	r Pro	Thr 4120	Pro	Thr	Gly	7 Thr	Gln 4125		: Pro) Thr
Thr	Thr 4130	Pro) Ile	e Thr	Thi	Thr 4135	Thr	Thr	Val	Thr	Pro 4140		Pro	Thr
Pro	Thr 4145	Gly	7 Thr	Glr	ı Thr	Pro 4150	Thr		Thr	Pro	Ile 4155		Thr	Thr
Thr	Thr 4160	Val	Thr	Pro	Thr	Pro 4165	Thr	Pro	Thr	Gly	Thr 4170		Thr	Pro
Thr	Thr 4175	Thr	Pro	Ile	Thr	Thr 4180	Thr	Thr	Thr	Val	Thr 4185		Thr	Pro
Thr	Pro 4190	Thr	Gly	Thr	Gln	Thr 4195	Gly	Pro	Pro	Thr	His 4200		Ser	Thr
Ala	Pro 4205	Ile	Ala	Glu	Leu	Thr 4210	Thr	Ser	Asn	Pro	Pro 4215		Glu	Ser
Ser	Thr 4220	Pro	Gln	Thr	Ser	Arg 4225	Ser	Thr	Ser	Ser	Pro 4230	Leu	Thr	Glu
Ser	Thr 4235	Thr	Leu	Leu	Ser	Thr 4240	Leu	Pro	Pro	Ala	Ile 4245	Glu	Met	Thr
Ser	Thr 4250	Ala	Pro	Pro	Ser	Thr 4255	Pro	Thr	Ala	Pro	Thr 4260	Thr	Thr	Ser
Gly	Gly 4265	His	Thr	Leu	Ser	Pro 4270	Pro	Pro	Ser	Thr	Thr 4275	Thr	Ser	Pro
Pro (Gly 4280	Thr	Pro	Thr	Arg	Gly 4285	Thr	Thr	Thr		Ser 4290	Ser	Ser	Ala
Pro 1	Thr 4295	Pro	Ser	Thr	Val	Gln 4300	Thr	Thr	Thr		Ser 4305	Ala	Trp	Thr

Pro	Thr 4310	Pro	Thr	Pro	Leu	Ser 4315	Thr	Pro	Ser	Ile	Ile 4320	Arg	Thr	Thr
Gly	Leu 4325	Arg	Pro	Tyr	Pro	Ser 4330	Ser	Val	Leu	Ile	Cys 4335	Cys	Val	Leu
Asn	Asp 4340		Tyr	Tyr	Ala	Pro 4345	Gly	Glu	Glu	Val	Tyr 4350	Asn	Gly	Thr
Tyr	Gly 4355		Thr	Cys	Tyr	Phe 4360	Val	Asn	Cys	Ser	Leu 4365	Ser	Cys	Thr
Leu	Glu 4370		Tyr	Asn	Trp	Ser 4375	Cys	Pro	Ser	Thr	Pro 4380	Ser	Pro	Thr
Pro	Thr 4385		Ser	Lys	Ser	Thr 4390		Thr	Pro	Ser	Lys 4395	Pro	Ser	Ser
Thr	Pro 4400		Lys	Pro	Thr	Pro 4405		Thr	Lys	Pro	Pro 4410	Glu	Cys	Pro
Asp	Phe 4415		Pro	Pro	Arg	Gln 4420	Glu	Asn	Glu	Thr	Trp 4425	Trp	Leu	Cys
Asp	Cys 4430		Met	Ala	Thr	Cys 4435	Lys	Tyr	Asn	Asn	Thr 4440	Val	Glu	Ile
Val	Lys 4445		Glu	. Cys		Pro 4450		Pro	Met	Pro	Thr 4455	Сув	Ser	Asn
	Leu 4460		Pro	Val	Arg	Val 4465	Glu	Asp	Pro	Asp	Gly 4470	Суѕ	Cys	Trp
His	Trp		ı Cys	: Asp	Cys	Tyr 4480	Су <i>в</i>)	: Thr	Gly	Trp	Gly 4485	Asp	Pro	His
Туг	Val 4490		r Phe	e Asp	Gly	Leu 4495	Tyr 5	туг	s Ser	Tyr	Gln 4500	Gly	Asn	Cys
Thi	Tyr 450		L Lei	ı Val	Glu	ı Glu 451(e Sei	r Pro	Ser	Val 4515	Asp	Asn	Phe
G17	y Val 4520		c Ile	e Asp	o Asr	1 Tyr 452		з Суа	s Asp	Pro	Asn 4530	Asp)	Lys	Val

Ser	Cys 453	Pro 5	Arg	J Thr	Leu	1 Ile 4540	Va]	. Arg	y His	Glu	1 Thr 4545		n Glu	ı Val
Leu	ı Ile 455(Lys)	: Thr	Val	. His	Met 4555	Met	: Pro) Met	Glr	Val 4560		ı Val	Gln
Val	Asn 4565	Arg	g Gln	Ala	. Val	Ala 4570	Leu)	Pro	Tyr	. Tàs	Lys 4575		Gly	Leu
Glu	Val 4580	Tyr	Gln	. Ser	Gly	Ile 4585	Asn	Туг	· Val	Val	Asp 4590		Pro	Glu
Leu	Gly 4595	Val	Leu	Val	Ser	Tyr 4600	Asn	Gly	Leu	Ser	Phe 4605		Val	Arg
Leu	Pro 4610	Tyr	His	Arg	Phe	Gly 4615	Asn	Asn	Thr	Lys	Gly 4620		Cys	Gly
Thr	Cys 4625	Thr	Asn	Thr	Thr	Ser 4630	Asp	Asp	Cys	Ile	Leu 4635		Ser	Gly
Glu	Ile 4640	Val	Ser	Asn	Cys	Glu 4645		Ala	Ala	Asp	Gln 4650		Leu	Val
Asn	Asp 4655	Pro	Ser	Lys	Pro	His 4660	Cys	Pro	His	Ser	Ser 4665	Ser	Thr	Thr
Lys	Arg 4670	Pro	Ala	Val	Thr	Val 4675	Pro	Gly	Gly	Gly	Lys 4680	Thr	Thr	Pro
His	Lys 4685			Thr		Ser 4690	Pro	Leu	Cys	Gln	Leu 4695	Ile	Lys	Asp
Ser	Leu 4700	Phe	Ala	Gln	Cys	His 4705	Ala	Leu	Val	Pro	Pro 4710	Gln	His	Tyr
Tyr	Asp 4715	Ala	Cys	Val	Phe	Asp 4720	Ser	Cys	Phe	Met	Pro 4725	Gly	Ser	Ser
Leu	Glu 4730	Cys	Ala	Ser	Leu	Gln 4735	Ala	Tyr	Ala	Ala	Leu 4740	Cys	Ala	Gln
Gln	Asn	Ile	Cys	Leu	Asp	Trp	Arg	Asn	Hìs	Thr	His	Gly	Ala	Cys

4745	4750	4755

Leu	Val 4760	Glu	Cys	Pro	Ser	His 4765		Glu	Tyr	Gln	Ala 4770		Gly	Pro
Ala	Glu 4775	Glu	Pro	Thr	Cys	Lys 4780		Ser	Ser	Ser	Gln 4785		Asn	Asn
Thr	Val 4790	Leu	Val	Glu	Gly	Cys 4795		Cys	Pro	Glu	Gly 4800		Met	Asn
Tyr	Ala 4805	Pro	Gly	Phe	Asp	Val 4810		Val	Lys	Thr	Cys 4815		Cys	Val
Gly	Pro 4820	Asp	Asn	Val	Pro	Arg 4825	Glu	Phe	Gly	Glu	His 4830		Glu	Phe
Asp	Cys 4835	Lys	Asn	Cys	Val	Cys 4840	Leu	Glu	Gly	Gly	Ser 4845	Gly	Ile	Ile
Cys	Gln 4850	Pro	Lys	Arg	Cys	Ser 4855	Gln	Lys	Pro	Val	Thr 4860		Cys	Val
Glu	Asp 4865		Thr	Tyr	Leu	Ala 4870	Thr	Glu	Val	Asn	Pro 4875	Ala	Asp	Thr
Cys	Cys 4880	Asn	Ile	Thr	Val	Cys 4885	Lys	Cys	Asn	Thr	Ser 4890	Leu	Cys	Lys
Glu	Lys 4895	Pro	Ser	Val	Cys	Pro 4900	Leu	Gly	Phe	Glu	Val 4905	Lys	Ser	Lys
Met	Val 4910	Pro	Gly	Arg	Cys	Cys 4915	Pro	Phe	Tyr	Trp	Cys 4920	Glu	Ser	Lys
Gly	Val 4925	Суѕ	Val	His	Gly	Asn 4930	Ala	Glu	Tyr	Gln	Pro 4935	Gly	Ser	Pro
Val	Tyr 4940	Ser	Ser	Lys	Cys	Gln 4945	Asp	Cys	Val	Cys	Thr 4950	Asp	Lys	Val
Asp	Asn 4955	Asn	Thr	Leu	Leu	Asn 4960	Val	Ile	Ala	Cys	Thr 4965	His	Val	Pro

Cys	Asn 4970	Thr	Ser	Cys	Ser	Pro 4975	Gly	Phe	Glu	Leu	Met 4980		Ala	Pro
Gly	Glu 4985	Cys	Cys	Lys	Lys	Cys 4990	Glu	Gln	Thr	His	Cys 4995		Ile	Lys
Arg	Pro 5000		Asn	Gln	His	Val 5005		Leu	Lys	Pro	Gly 5010		Phe	Lys
Ser	Asp 5015	Pro	Lys	Asn	Asn	Cys 5020		Phe	Phe	Ser	Cys 5025		Lys	Ile
His	Asn 5030	Gln	Leu	Ile	Ser	Ser 5035	Val	Ser	Asn	Ile	Thr 5040	Cys	Pro	Asn
Phe	Asp 5045	Ala	Ser	Ile	Cys	Ile 5050	Pro	Gly	Ser	Ile	Thr 5055		Met	Pro
Asn	Gly 5060	Cys	Cys	Lys	Thr	Cys 5065	Thr	Pro	Arg	Asn	Glu 5070	Thr	Arg	Val
Pro	Cys 5075	Ser	Thr	Val	Pro	Val 5080	Thr	Thr	Glu	Val	Ser 5085	Туг	Ala	Gly
Cys	Thr 5090	Lys	Thr	Val	Leu	Met 5095	Asn	His	Cys	Ser	Gly 5100	Ser	Cys	Gly
Thr	Phe 5105	Val	Met	Tyr	Ser	Ala 5110	Lys	Ala	Gln	Ala	Leu 5115	Asp	His	Ser
Cys	Ser 5120										Arg 5130		Val	Val.
Leu	Ser 5135	Cys	Pro	Asn	Gly	Gly 5140	Ser	Leu	Thr	His	Thr 5145	Tyr	Thr	His
Ile	Glu 5150	Ser	Cys	Gln	Cys	Gln 5155	Asp	Thr	Val	Cys	Gly 5160	Leu	Pro	Thr
Gly	Thr 5165	Ser	Arg	Arg	Ala	Arg 5170	Arg	Ser	Pro	Arg	His 5175	Leu	Gly	Ser
Glv														

Gly

372/439

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<211> 878

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<213> Human

<400> 152

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Ser Ile Pro Thr Asp Ile Ser Ser Leu Pro Thr Pro Ile His Ile Ile 65 70 75 80

Ser Ser Ser Pro Ser Ile Gln Ser Thr Glu Thr Ser Ser Leu Val Gly 85 90 95

Thr Thr Ser Pro Thr Met Ser Thr Val Arg Ala Thr Leu Arg Ser Thr 100 105 110

Glu Asn Thr Pro Ile Ser Ser Phe Ser Thr Ser Ile Val Val Thr Pro 115 120 125

Glu Thr Pro Thr Thr Gln Ala Pro Pro Val Leu Met Ser Ala Thr Gly 130 135 140

Thr Gln Thr Ser Pro Val Pro Thr Thr Val Thr Phe Gly Ser Met Asp 145 150 155 160

Ser Ser Thr Ser Thr Leu His Thr Leu Thr Pro Ser Thr Ala Leu Ser 165 170 175

Lys Ile Met Ser Thr Ser Gln Phe Pro Ile Pro Ser Thr His Ser Ser 180 185 190

Thr Leu Gln Thr Thr Pro Ser Ile Pro Ser Leu Gln Thr Ser Leu Thr
195 200 205

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Ser Thr Ser Glu Phe Thr Thr Glu Ser Phe Thr Arg Gly Ser Thr Ser 215 Thr Asn Ala Ile Leu Thr Ser Phe Ser Thr Ile Ile Trp Ser Ser Thr 235 230 Pro Thr Ile Ile Met Ser Ser Ser Pro Ser Ser Ala Ser Ile Thr Pro 250 Val Phe Ala Thr Thr Ile His Ser Val Pro Ser Ser Pro Tyr Ile Phe 265 260 Ser Thr Glu Asn Val Gly Ser Ala Ser Ile Thr Ala Phe Pro Ser Leu 280 275 Ser Ser Ser Ser Thr Thr Ser Thr Ser Pro Thr Ser Ser Ser Leu Thr 295 290 Thr Ala Leu Thr Glu Ile Thr Pro Phe Ser Tyr Ile Ser Leu Pro Ser 310 305 Thr Thr Pro Cys Pro Gly Thr Ile Thr Ile Thr Ile Val Pro Ala Ser 330 325 Pro Thr Asp Pro Cys Val Glu Met Asp Pro Ser Thr Glu Ala Thr Ser 345 340 Pro Pro Thr Thr Pro Leu Thr Val Phe Pro Phe Thr Thr Glu Met Val 360 355 Thr Cys Pro Ser Ser Ile Ser Met Gln Thr Thr Leu Ala Thr His Met 370 375 Asp Thr Ser Ser Met Thr Pro Glu Ser Glu Ser Ser Ile Ile Pro Asn 390 395 385 Ala Ser Ser Ser Thr Gly Thr Gly Thr Val Pro Thr Asn Thr Val Phe 415 405 410 Thr Ser Thr Arg Leu Pro Thr Ser Glu Thr Trp Leu Ser Asn Asn Ser 420 425 430 Val Ile Pro Thr Pro Leu Pro Gly Val Ser Thr Ile Pro Leu Thr Met 445 435

Lys Pro Ser Ser Ser Leu Pro Thr Ile Leu Arg Thr Ser Ser Lys Ser Thr His Pro Ser Pro Pro Thr Ala Arg Thr Ser Glu Thr Ser Val Ala 470 475 Thr Thr Gln Thr Pro Thr Thr Leu Thr Thr Arg Arg Thr Thr Pro Ile 485 490 Thr Ser Trp Met Thr Thr Gln Ser Thr Leu Thr Thr Ala Gly Thr 500 505 Cys Asp Asn Gly Gly Thr Trp Glu Gln Gly Gln Cys Ala Cys Leu Pro 515 520 Gly Phe Ser Gly Asp Arg Cys Gln Leu Gln Thr Arg Cys Gln Asn Gly 535 Gly Gln Trp Asp Gly Leu Lys Cys Gln Cys Pro Ser Thr Phe Tyr Gly 550 Ser Ser Cys Glu Phe Ala Val Glu Gln Val Asp Leu Asp Val Val Glu 570 Thr Glu Val Gly Met Glu Val Ser Val Asp Gln Gln Phe Ser Pro Asp 585 590 Leu Asn Asp Asn Thr Ser Gln Ala Tyr Arg Asp Phe Asn Lys Thr Phe 600 605 Trp Asn Gln Met Gln Lys Ile Phe Ala Asp Met Gln Gly Phe Thr Phe 615 620 Lys Gly Val Glu Ile Leu Ser Leu Arg Asn Gly Ser Ile Val Val Asp 630 635 Tyr Leu Val Leu Glu Met Pro Phe Ser Pro Gln Leu Glu Ser Glu 645 650 Tyr Glu Gln Val Lys Thr Thr Leu Lys Glu Gly Leu Gln Asn Ala Ser 660 665 670 Gln Asp Ala Asn Ser Cys Gln Asp Ser Gln Thr Leu Cys Phe Lys Pro

675 680 685

Asp Ser Ile Lys Val Asn Asn Asn Ser Lys Thr Glu Leu Thr Pro Glu 690 695 700

Ala Ile Cys Arg Arg Ala Ala Pro Thr Gly Tyr Glu Glu Phe Tyr Phe 705 710 715 720

Pro Leu Val Glu Ala Thr Arg Leu Arg Cys Val Thr Lys Cys Thr Ser 725 730 735

Gly Val Asp Asn Ala Ile Asp Cys His Gln Gly Gln Cys Val Leu Glu 740 745 750

Thr Ser Gly Pro Ala Cys Arg Cys Tyr Ser Thr Asp Thr His Trp Phe 755 760 765

Ser Gly Pro Arg Cys Glu Val Ala Val His Trp Arg Ala Leu Val Gly 770 780

Gly Leu Thr Ala Gly Ala Ala Leu Leu Val Leu Leu Leu Leu Ala Leu 785 790 795 800

Gly Val Arg Ala Val Arg Ser Gly Trp Trp Gly Gly Gln Arg Arg Gly 805 810 815

Arg Ser Trp Asp Gln Asp Arg Lys Trp Phe Glu Thr Trp Asp Glu Glu 820 825 830

Val Val Gly Thr Phe Ser Asn Trp Gly Phe Glu Asp Asp Gly Thr Asp 835 840 845

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Lys Val His Ile Lys Arg Pro Glu Met Thr Ser Ser Ser Val 865 870 875

<210> 153

<211> 1938

<212> PRT

<213> Human

<400> 153

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Leu Arg Lys Pro Glu Lys Glu Arg Ile Glu Ala Gln Asn Arg Pro Phe 20 25 30

Asp Ser Lys Lys Ala Cys Phe Val Ala Asp Asn Lys Glu Met Tyr Val 35 40 45

Lys Gly Met Ile Gln Thr Arg Glu Asn Asp Lys Val Ile Val Lys Thr 50 60

Leu Asp Asp Arg Met Leu Thr Leu Asn Asp Gln Val Phe Pro Met 65 70 75 80

Asn Pro Pro Lys Phe Asp Lys Ile Glu Asp Met Ala Met Met Thr His 85 90 95

Leu His Glu Pro Ala Val Leu Tyr Asn Leu Lys Glu Arg Tyr Ala Ala 100 105 110

Trp Met Ile Tyr Thr Tyr Ser Gly Leu Phe Cys Val Thr Val Asn Pro 115 120 125

Tyr Lys Trp Leu Pro Val Tyr Lys Pro Glu Val Val Ala Ala Tyr Arg 130 135 140

Gly Lys Lys Arg Gln Glu Ala Pro Pro His Ile Phe Ser Ile Ser Asp 145 150 155 160

Asn Ala Tyr Gln Phe Met Leu Thr Asp Arg Asp Asn Gln Ser Ile Leu 165 170 175

Ile Thr Gly Glu Ser Gly Ala Gly Lys Thr Val Asn Thr Lys Arg Val
180 185 190

Ile Gln Tyr Phe Ala Thr Ile Ala Val Thr Gly Asp Lys Lys Glu
195 200 205

Thr Gln Pro Gly Lys Met Gln Gly Thr Leu Glu Asp Gln Ile Ile Gln 210 215 220

Ala Asn Pro Leu Leu Glu Ala Phe Gly Asn Ala Lys Thr Val Arg Asn 225 230 235 240

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Asp Asn Ser Ser Arg Phe Gly Lys Phe Ile Arg Ile His Phe Gly Ala 245 250 Thr Gly Lys Leu Ala Ser Ala Asp Ile Glu Thr Tyr Leu Leu Glu Lys 265 Ser Arg Val Thr Phe Gln Leu Ser Ser Glu Arg Ser Tyr His Ile Phe 275 280 Tyr Gln Ile Met Ser Asn Lys Lys Pro Glu Leu Ile Asp Leu Leu 295 Ile Ser Thr Asn Pro Phe Asp Phe Pro Phe Val Ser Gln Gly Glu Val 315 Thr Val Ala Ser Ile Asp Asp Ser Glu Glu Leu Leu Ala Thr Asp Asn 330 Ala Ile Asp Ile Leu Gly Phe Ser Ser Glu Glu Lys Val Gly Ile Tyr 345 Lys Leu Thr Gly Ala Val Met His Tyr Gly Asn Met Lys Phe Lys Gln 360 Lys Gln Arg Glu Glu Gln Ala Glu Pro Asp Gly Thr Glu Val Ala Asp 375 380 Lys Ala Gly Tyr Leu Met Gly Leu Asn Ser Ala Glu Met Leu Lys Gly 390 395 Leu Cys Cys Pro Arg Val Lys Val Gly Asn Glu Tyr Val Thr Lys Gly 405 415 Gln Asn Val Gln Gln Val Thr Asn Ser Val Gly Ala Leu Ala Lys Ala 420 430 Val Tyr Glu Lys Met Phe Leu Trp Met Val Thr Arg Ile Asn Gln Gln 440 445 Leu Asp Thr Lys Gln Pro Arg Gln Tyr Phe Ile Gly Val Leu Asp Ile 455 460 Ala Gly Phe Glu Ile Phe Asp Phe Asn Ser Leu Glu Gln Leu Cys Ile 470 475

Asn	Phe	Thr	Asn	Glu 485	Lys	Leu	Gln	Gln	Phe 490	Phe	Asn	His	His	Met 495	Phe
Val	Leu	Glu	Gln 500	Glu	Glu	Tyr	Lys	Lys 505	Glu	Gly	Ile	Glu	Trp 510	Glu	Phe
Ile	Asp	Phe 515	Gly	Met	Asp	Leu	Ala 520	Ala	Cys	Ile	Glu	Leu 525	Ile	Glu	Lys
Pro	Met 530	Gly	Ile	Phe	Ser	Ile 535	Leu	Glu	Glu	Glu	Cys 540	Met	Phe	Pro	Lys
Ala 545	Thr	Asp	Thr	Ser	Phe 550	Lys	Asn	Lys	Leu	Tyr 555	Asp	Gln	His	Leu	Gly 560
Lys	Ser	Asn	Asn	Phe 565	Gln	Lys	Pro	Lys	Pro 570	Ala	Lys	Gly	Lys	Ala 575	Glu
Ala	His	Phe	Ser 580	Leu	Val	His	Tyr	Ala 585	Gly	Thr	Val	Asp	Tyr 590	Asn	Ile
Ala	Gly	Trp 595	Leu	Asp	Lys	Asn	Lys 600	Asp	Pro	Leu	Asn	Glu 605	Thr	Val	Val
Gly	Leu 610	Tyr	Gln	Lys	Ser	Ser 615	Leu	Lys	Leu	Leu	Ser 620	Phe	Leu	Phe	Ser
Asn 625	Tyr	Ala	Gly	Ala	Glu 630	Thr	Gly	Asp	Ser	Gly 635	Gly	Ser	Lys	Lys	Gly 640
Gly	Lys	Lys	Lys	Gly 645	Ser	Ser	Phe	Gln	Thr 650		Ser			Phe 655	Arg
Glu	Asn	Leu	Asn 660	Lys	Leu	Met	Thr	Asn 665	Leu	Arg	Ser	Thr	His 670	Pro	His
Phe	Val	Arg 675	Cys	Leu	Ile	Pro	Asn 680	Glu	Thr	Lys	Thr	Pro 685	Gly	Val	Met
Asp	His 690	Tyr	Leu	Val	Met	His 695	Gln	Leu	Arg	Cys	Asn 700	Gly	Val	Leu	Glu
Gly 705	Ile	Arg	Ile	Cys	Arg 710	Lys	Gly	Phe	Pro	Ser 715	Arg	Ile	Leu	Tyr	Ala 720

Asp Phe Lys Gln Arg Tyr Arg Ile Leu Asn Ala Ser Ala Ile Pro Glu 725 Gly Gln Phe Ile Asp Ser Lys Asn Ala Ser Glu Lys Leu Leu Asn Ser Ile Asp Val Asp Arg Glu Gln Phe Arg Phe Gly Asn Thr Lys Val Phe 760 Phe Lys Ala Gly Leu Leu Gly Leu Leu Glu Glu Met Arg Asp Glu Lys Leu Val Thr Leu Met Thr Ser Thr Gln Ala Val Cys Arg Gly Tyr Leu Met Arg Val Glu Phe Lys Lys Met Met Glu Arg Arg Asp Ser Ile Phe Cys Ile Gln Tyr Asn Ile Arg Ser Phe Met Asn Val Lys His Trp Pro 825 Trp Met Asn Leu Phe Phe Lys Ile Lys Pro Leu Lys Ser Ala Glu 840 Ala Glu Lys Glu Met Ala Thr Met Lys Glu Asp Phe Glu Arg Thr Lys 855 Glu Glu Leu Ala Arg Ser Glu Ala Arg Arg Lys Glu Leu Glu Glu Lys 870 875 Met Val Ser Leu Gln Glu Lys Asn Asp Leu Gln Leu Gln Val Gln 890 885 Ser Glu Thr Glu Asn Leu Met Asp Ala Glu Glu Arg Cys Glu Gly Leu 900 Ile Lys Ser Lys Ile Leu Leu Glu Ala Lys Val Lys Glu Leu Thr Glu Arg Leu Glu Glu Glu Glu Met Asn Ser Glu Leu Val Ala Lys Lys 935 Arg Asn Leu Glu Asp Lys Cys Ser Ser Leu Lys Arg Asp Ile Asp Asp

945 950 955 960

Leu Glu Leu Thr Leu Thr Lys Val Glu Lys Glu Lys His Ala Thr Glu 965 970 975

Asn Lys Val Lys Asn Leu Ser Glu Glu Met Thr Ala Leu Glu Glu Asn 980 985 990

Ile Ser Lys Leu Thr Lys Glu Lys Lys Ser Leu Gln Glu Ala His Gln 995 1000 1005

Gln Thr Leu Asp Asp Leu Gln Val Glu Glu Asp Lys Val Asn Gly 1010 $$ 1020

Leu Ile Lys Ile Asn Ala Lys Leu Glu Gln Gln Thr Asp Asp Leu 1025 1035

Glu Gly Ser Leu Glu Gln Glu Lys Lys Leu Arg Ala Asp Leu Glu 1040 1045 1050

Arg Ala Lys Arg Lys Leu Glu Gly Asp Leu Lys Met Ser Gln Glu 1055 1060 1065

Ser Ile Met Asp Leu Glu Asn Glu Lys Gln Gln Ile Glu Glu Lys 1070 1080

Leu Lys Lys Lys Glu Phe Glu Leu Ser Gln Leu Gln Ala Arg Ile 1085 1090 1095

Asp Asp Glu Gln Val His Ser Leu Gln Phe Gln Lys Lys Ile Lys 1100 1105 1110

Glu Leu Gln Ala Arg Ile Glu Glu Leu Glu Glu Glu Ile Glu Ala 1115 1120 1125

Glu His Thr Leu Arg Ala Lys Ile Glu Lys Gln Arg Ser Asp Leu 1130 1140

Ala Arg Glu Leu Glu Glu Ile Ser Glu Arg Leu Glu Glu Ala Ser 1145 1150 1155

Gly Ala Thr Ser Ala Gln Ile Glu Met Asn Lys Lys Arg Glu Ala 1160 1165 1170

Glu	Phe 1175		Lys	Met	Arg	Arg 1180		Leu	Glu	Glu	Ala 1185		Leu	Gln
His	Glu 1190	Ala	Thr	Ala	Ala	Thr 1195	Leu	Arg	Lys	Lys	Gln 1200	Ala	Asp	Ser
Val	Ala 1205	Glu	Leu	Gly	Glu	Gln 1210		Asp	Asn	Leu	Gln 1215		Val	Lys
Gln	Lys 1220	Leu	Glu	Lys	Glu	Lys 1225		Glu	Leu	Lys	Met 1230		Ile	Asp
Asp	Met 1235		Ser	Asn	Ile	Glu 1240		Leu	Ser	Lys	Ser 1245	Lys	Ser	Asn
Ile	Glu 1250	Arg	Thr	Cys	Arg	Thr 1255	Val	Glu	Asp	Gln	Phe 1260		Glu	Ile
Lys	Ala 1265	Lys	Asp	Glu	Gln	Gln 1270		Gln	Leu	Ile	His 1275	Asp	Leu	Asn
Met	Gln 1280	Lys	Ala	Arg	Leu	Gln 1285		Gln	Asn	Gly	Glu 1290	Leu	Ser	His
Arg	Val 1295	Glu	Glu	Lys	Glu	Ser 1300	Leu	Ile	Ser	Gln	Leu 1305	Thr	Lys	Ser
Lys	Gln 1310		Leu	Thr	Gln	Gln 1315	Leu	Glu	Glu	Leu	Lys 1320	Arg	Gln	Met
Glu											His 1335	Ala	Leu	Gln
Ser	Ser 1340	Arg	His	Asp	Cys	Asp 1345	Leu	Leu	Arg	Glu	Gln 1350	Tyr	Glu	Glu
Glu	Gln 1355	Glu	Ala	Lys	Ala	Glu 1360	Leu	Gln	Arg	Ala	Leu 1365	Ser	Lys	Ala
Asn	Ser 1370	Glu	Val	Ala	Gln	Trp 1375	Lys	Thr	Lys	Tyr	Glu 1380	Thr	Asp	Ala
Ile	Gln 1385	Arg	Thr	Glu	Glu	Leu 1390	Glu	Glu	Ala	Lys	Lys 1395	Lys	Leu	Ala

Gln	Arg 1400	Leu	Gln	Glu	Ala	Glu 1405	Glu	Lys	Thr	Glu	Thr 1410		. Asn	. Ser
Lys	Cys 1415	Ala	Ser	Leu	Glu	Lys 1420		Lys	Gln	Arg	Leu 1425		. Gly	Glu
Val	Glu 1430		Leu	Met	Arg	Asp 1435		Glu	Arg	Ser	His 1440		Ala	Cys
Ala	Thr 1445	Leu	Asp	Lys	Lys	Gln 1450		Asn	Phe	Asp	Lys 1455		Leu	Ala
Glu	Trp 1460		Gln	Lys	Leu	Asp 1465		Ser	Gln	Ala	Glu 1470	Leu	Glu	Ala
Ala	Gln 1475	Lys	Glu	Ser	Arg	Ser 1480		Ser	Thr	Glu	Leu 1485	Phe	Lys	Met
Arg	Asn 1490	Ala	Tyr	Glu	Glu	Val 1495	Val	Asp	Gln	Leu	Glu 1500	Thr	Leu	Arg
Arg	Glu 1505	Asn	Lys	Asn	Leu	Gln 1510	Glu	Glu	Ile	Ser	Asp 1515	Leu	Thr	Glu
Gln	Ile 1520	Ala	Glu	Thr	Gly	Lys 1525	Asn	Leu	Gln	Glu	Ala 1530	Glu	Lys	Thr
Lys	Lys 1535	Leu	Val	Glu	Gln	Glu 1540	Lys	Ser	Asp	Leu	Gln 1545	Val	Ala	Leu
Glu	Glu 1550	Val	Glu	Gly	Ser	Leu 1555	Glu	His	Glu	Glu	Ser 1560	Lys	Ile	Leu
	Val 1565	Gln	Leu	Glu	Leu	Ser 1570	Gln	Val	Lys	Ser	Glu 1575	Leu	Asp	Arg
_	Val 1580	Ile	Glu	Lys	Asp	Glu 1585	Glu	Ile	Glu	Gln	Leu 1590	Lys	Arg	Asn
Ser	Gln 1595	Arg	Ala	Ala	Glu	Ala 1600	Leu	Gln	Ser		Leu 1605	Asp	Ala	Glu
Ile	Arg 1610	Ser	Arg	Asn	Asp	Ala 1615	Leu	Arg	Leu		Lys 1620	Lys	Met	Glu

Gly	Asp 1625	Leu	Asn	Glu	Met	Glu 1630		Gln	Leu	Gly	His 1635	Ser	Asn	Arg
Gln	Met 1640	Ala	Glu	Thr	Gln	Arg 1645	His	Leu	Arg	Thr	Val 1650	Gln	Gly	Gln
Leu	Lys 1655	Asp	Ser	Gln	Leu	His 1660	Leu	Asp	Asp	Ala	Leu 1665	Arg	Ser	Asn
Glu	Asp 1670	Leu	Lys	Glu	Gln	Leu 1675	Ala	Ile	Val	Glu	Arg 1680	Arg	Asn	Gly
Leu	Leu 1685		Glu	Glu	Leu	Glu 1690		Met	Lys	Val	Ala 1695	Leu	Glu	Gln
Thr	Glu 1700		Thr	Arg	Arg	Leu 1705		Glu	Gln	Glu	Leu 1710	Leu	Asp	Ala
Ser	Asp 1715		Val	Gln	Leu	Leu 1720		Ser	Gln	Asn	Thr 1725	Ser	Leu	Ile
Asn	Thr 1730		Lys	Lys	Leu	Glu 1735		Asp	Ile	Ala	Gln 1740		Gln	Ala
Glu	Val 1745		Asn	Ser	Ile	Gln 1750		Ser	Arg	Asn	Ala 1755		Glu	Lys
Ala	Lys 1760	_	Ala	Ile	Thr	Asp 1765		Ala	Met	Met	Ala 1770		Glu	Leu
_	Lys 1775							His			Arg 1785		Lys	Lys
Asn	Leu 1790		Gln	Thr	Val	Lys 1795		Leu	Gln	His	Arg 1800		Asp	Glu
Ala	Glu 1805		Leu	Ala	Leu	Lys 1810		Gly	Lys	Lys	Gln 1815		Gln	Lys
Leu	Glu 1820		Arg	Val	Arg	Glu 1825		Glu	Asn	Glu	Leu 1830		Val	Glu
Gln	Lys	Arg	. Gly	Ala	Glu	Ala	Leu	. Lys	Gly	Ala	His	Lys	Tyr	Glu

1835 1840 1845

Arg Lys Val Lys Glu Met Thr Tyr Gln Ala Glu Glu Asp Arg Lys 1850 1855 1860

Asn Ile Leu Arg Leu Gln Asp Leu Val Asp Lys Leu Gln Ala Lys 1865 1870 1875

Val Lys Ser Tyr Lys Arg Gln Ala Glu Glu Ala Glu Glu Gln Ala 1880 1885 1890

Asn Thr Gln Leu Ser Arg Cys Arg Arg Val Gln His Glu Leu Glu 1895 1900 1905

Glu Ala Ala Glu Arg Ala Asp Ile Ala Glu Ser Gln Val Asn Lys 1910 1915 1920

Leu Arg Ala Lys Ser Arg Asp Val Gly Ser Gln Lys Met Glu Glu 1925 1930 1935

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<211> 173

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<400> 154

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Gln Arg Ala Ser Ser Asn Val Phe Ser Asn Phe Glu Gln Thr Gln Ile 20 25 30

Gln Glu Phe Lys Glu Ala Phe Thr Leu Met Asp Gln Asn Arg Asp Gly 35 40 45

Phe Ile Asp Lys Glu Asp Leu Lys Asp Thr Tyr Ala Ser Leu Gly Lys 50 55 60

Thr Asn Val Lys Asp Asp Glu Leu Asp Ala Met Leu Lys Glu Ala Ser 65 70 75 80

Gly Pro Ile Asn Phe Thr Met Phe Leu Asn Leu Phe Gly Glu Lys Leu 85 90 95

Ser Gly Thr Asp Ala Glu Glu Thr Ile Leu Asn Ala Phe Lys Met Leu

100 105 110

Asp Pro Asp Gly Lys Gly Lys Ile Asn Lys Glu Tyr Ile Lys Arg Leu 115 120 125

Leu Met Ser Gln Ala Asp Lys Met Thr Ala Glu Glu Val Asp Gln Met 130 135 140

Phe Gln Phe Ala Ser Ile Asp Val Ala Gly Asn Leu Asp Tyr Lys Ala 145 150 155 160

Leu Ser Tyr Val Ile Thr His Gly Glu Glu Lys Glu Glu 165 170

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<212> PRT

<213> Human

<400> 155

Met Glu Thr Lys Gly Tyr His Ser Leu Pro Glu Gly Leu Asp Met Glu 1 5 10 15

Arg Arg Trp Gly Gln Val Ser Gln Ala Val Glu Arg Ser Ser Leu Gly 20 25 30

Pro Thr Glu Arg Thr Asp Glu Asn Asn Tyr Met Glu Ile Val Asn Val 35 40 45

Ser Cys Val Ser Gly Ala Ile Pro Asn Asn Ser Thr Gln Gly Ser Ser 50 60

Lys Glu Lys Gln Glu Leu Leu Pro Cys Leu Gln Gln Asp Asn Asn Arg 65 70 75 80

Pro Gly Ile Leu Thr Ser Asp Ile Lys Thr Glu Leu Glu Ser Lys Glu 85 90 95

Leu Ser Ala Thr Val Ala Glu Ser Met Gly Leu Tyr Met Asp Ser Val 100 105 110

Arg Asp Ala Asp Tyr Ser Tyr Glu Gln Gln Asn Gln Gln Gly Ser Met 115 120 125

Ser Pro Ala Lys Ile Tyr Gln Asn Val Glu Gln Leu Val Lys Phe Tyr

130 135 140

Lys Gly Asn Gly His Arg Pro Ser Thr Leu Ser Cys Val Asn Thr Pro 145 150 155 160

Leu Arg Ser Phe Met Ser Asp Ser Gly Ser Ser Val Asn Gly Gly Val 165 170 175

Met Arg Ala Ile Val Lys Ser Pro Ile Met Cys His Glu Lys Ser Pro 180 185 190

Ser Val Cys Ser Pro Leu Asn Met Thr Ser Ser Val Cys Ser Pro Ala 195 200 205

Gly Ile Asn Ser Val Ser Ser Thr Thr Ala Ser Phe Gly Ser Phe Pro 210 215 220

Val His Ser Pro Ile Thr Gln Gly Thr Pro Leu Thr Cys Ser Pro Asn 225 230 235 240

Ala Glu Asn Arg Gly Ser Arg Ser His Ser Pro Ala His Ala Ser Asn 245 250 255

Val Gly Ser Pro Leu Ser Ser Pro Leu Ser Ser Met Lys Ser Ser Ile 260 265 270

Ser Ser Pro Pro Ser His Cys Ser Val Lys Ser Pro Val Ser Ser Pro 275 280 285

Asn Asn Val Thr Leu Arg Ser Ser Val Ser Ser Pro Ala Asn Ile Asn 290 295 300

Asn Ser Arg Cys Ser Val Ser Ser Pro Ser Asn Thr Asn Asn Arg Ser 305 310 315 320

Thr Leu Ser Ser Pro Ala Ala Ser Thr Val Gly Ser Ile Cys Ser Pro 325

Val Asn Asn Ala Phe Ser Tyr Thr Ala Ser Gly Thr Ser Ala Gly Ser 340 345 350

Ser Thr Leu Arg Asp Val Val Pro Ser Pro Asp Thr Gln Glu Lys Gly 355 360 365

Ala Gln Glu Val Pro Phe Pro Lys Thr Glu Glu Val Glu Ser Ala Ile 370 375 380

Ser Asn Gly Val Thr Gly Gln Leu Asn Ile Val Gln Tyr Ile Lys Pro 385 390 395 400

Glu Pro Asp Gly Ala Phe Ser Ser Ser Cys Leu Gly Gly Asn Ser Lys 405 410 415

Ile Asn Ser Asp Ser Ser Phe Ser Val Pro Ile Lys Gln Glu Ser Thr 420 425 430

Lys His Ser Cys Ser Gly Thr Ser Phe Lys Gly Asn Pro Thr Val Asn 435 440 445

Pro Phe Pro Phe Met Asp Gly Ser Tyr Phe Ser Phe Met Asp Asp Lys 450 455 460

Asp Tyr Tyr Ser Leu Ser Gly Ile Leu Gly Pro Pro Val Pro Gly Phe 465 470 475 480

Asp Gly Asn Cys Glu Gly Ser Gly Phe Pro Val Gly Ile Lys Gln Glu 485 490 495

Pro Asp Asp Gly Ser Tyr Tyr Pro Glu Ala Ser Ile Pro Ser Ser Ala 500 505 510

Ile Val Gly Val Asn Ser Gly Gly Gln Ser Phe His Tyr Arg Ile Gly 515 520 525

Ala Gln Gly Thr Ile Ser Leu Ser Arg Ser Ala Arg Asp Gln Ser Phe 530 540

Gln His Leu Ser Ser Phe Pro Pro Val Asn Thr Leu Val Glu Ser Trp 545 550 555 560

Lys Ser His Gly Asp Leu Ser Ser Arg Arg Ser Asp Gly Tyr Pro Val 565 570 575

Leu Glu Tyr Ile Pro Glu Asn Val Ser Ser Ser Thr Leu Arg Ser Val 580 585 590

Ser Thr Gly Ser Ser Arg Pro Ser Lys Ile Cys Leu Val Cys Gly Asp 595 600 605

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Glu Ala Ser Gly Cys His Tyr Gly Val Val Thr Cys Gly Ser Cys Lys 610 615 620

Val Phe Phe Lys Arg Ala Val Glu Gly Gln His Asn Tyr Leu Cys Ala 625 630 635 640

Gly Arg Asn Asp Cys Ile Ile Asp Lys Ile Arg Arg Lys Asn Cys Pro 645 650 655

Ala Cys Arg Leu Gln Lys Cys Leu Gln Ala Gly Met Asn Leu Gly Ala 660 665 670

Arg Lys Ser Lys Lys Leu Gly Lys Leu Lys Gly Ile His Glu Glu Gln 675 680 685

Pro Gln Gln Gln Gln Pro Pro Pro Pro Pro Pro Pro Pro Gln Ser Pro 690 700

Glu Glu Gly Thr Thr Tyr Ile Ala Pro Ala Lys Glu Pro Ser Val Asn 705 710 715 720

Thr Ala Leu Val Pro Gln Leu Ser Thr Ile Ser Arg Ala Leu Thr Pro 725 730 735

Ser Pro Val Met Val Leu Glu Asn Ile Glu Pro Glu Ile Val Tyr Ala 740 745 750

Gly Tyr Asp Ser Ser Lys Pro Asp Thr Ala Glu Asn Leu Leu Ser Thr 755 760 765

Leu Asn Arg Leu Ala Gly Lys Gln Met Ile Gln Val Val Lys Trp Ala 770 780

Lys Val Leu Pro Gly Phe Lys Asn Leu Pro Leu Glu Asp Gln Ile Thr 785 790 795 800

Leu Ile Gln Tyr Ser Trp Met Cys Leu Ser Ser Phe Ala Leu Ser Trp 805 810 815

Arg Ser Tyr Lys His Thr Asn Ser Gln Phe Leu Tyr Phe Ala Pro Asp 820 825 830

Leu Val Phe Asn Glu Glu Lys Met His Gln Ser Ala Met Tyr Glu Leu 835 840 845

Cys Gln Gly Met His Gln Ile Ser Leu Gln Phe Val Arg Leu Gln Leu 850 860

Thr Phe Glu Glu Tyr Thr Ile Met Lys Val Leu Leu Leu Leu Ser Thr 865 870 875 880

Ile Pro Lys Asp Gly Leu Lys Ser Gln Ala Ala Phe Glu Glu Met Arg 885 890 895

Thr Asn Tyr Ile Lys Glu Leu Arg Lys Met Val Thr Lys Cys Pro Asn 900 905 910

Asn Ser Gly Gln Ser Trp Gln Arg Phe Tyr Gln Leu Thr Lys Leu Leu 915 920 925

Asp Ser Met His Asp Leu Val Ser Asp Leu Leu Glu Phe Cys Phe Tyr 930 935 940

Thr Phe Arg Glu Ser His Ala Leu Lys Val Glu Phe Pro Ala Met Leu 945 950 955 960

Val Glu Ile Ile Ser Asp Gln Leu Pro Lys Val Glu Ser Gly Asn Ala 965 970 975

Lys Pro Leu Tyr Phe His Arg Lys 980

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<211> 495

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<213> Human

<400> 156

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Gly Leu Thr Pro Ile Val Ser Gln Phe Lys Met Val Asn Tyr Ser Tyr 20 25 30

Asp Glu Asp Leu Glu Glu Leu Cys Pro Val Cys Gly Asp Lys Val Ser 35 40 45

Gly Tyr His Tyr Gly Leu Leu Thr Cys Glu Ser Cys Lys Gly Phe Phe 50 55 60

Lys Arg Thr Val Gln Asn Asn Lys Arg Tyr Thr Cys Ile Glu Asn Gln 70 Asn Cys Gln Ile Asp Lys Thr Gln Arg Lys Arg Cys Pro Tyr Cys Arg Phe Gln Lys Cys Leu Ser Val Gly Met Lys Leu Glu Ala Val Arg Ala 105 Asp Arg Met Arg Gly Gly Arg Asn Lys Phe Gly Pro Met Tyr Lys Arg 120 Asp Arg Ala Leu Lys Gln Gln Lys Lys Ala Leu Ile Arg Ala Asn Gly 135 Leu Lys Leu Glu Ala Met Ser Gln Val Ile Gln Ala Met Pro Ser Asp 155 150 160 Leu Thr Ile Ser Ser Ala Ile Gln Asn Ile His Ser Ala Ser Lys Gly 165 170 Leu Pro Leu Asn His Ala Ala Leu Pro Pro Thr Asp Tyr Asp Arg Ser 180 185 Pro Phe Val Thr Ser Pro Ile Ser Met Thr Met Pro Pro His Gly Ser 195 200 Leu Gln Gly Tyr Gln Thr Tyr Gly His Phe Pro Ser Arg Ala Ile Lys Ser Glu Tyr Pro Asp Pro Tyr Thr Ser Ser Pro Glu Ser Ile Met Gly Tyr Ser Tyr Met Asp Ser Tyr Gln Thr Ser Ser Pro Ala Ser Ile Pro 245 250 His Leu Ile Leu Glu Leu Lys Cys Glu Pro Asp Glu Pro Gln Val Gln Ala Lys Ile Met Ala Tyr Leu Gln Glu Gln Ala Asn Arg Ser 275 280 285 Lys His Glu Lys Leu Ser Thr Phe Gly Leu Met Cys Lys Met Ala Asp

290 295 300

Gln Thr Leu Phe Ser Ile Val Glu Trp Ala Arg Ser Ser Ile Phe Phe 305 310 315 320

Arg Glu Leu Lys Val Asp Asp Gln Met Lys Leu Leu Gln Asn Cys Trp 325 330 335

Ser Glu Leu Leu Ile Leu Asp His Ile Tyr Arg Gln Val Val His Gly 340 345 350

Lys Glu Gly Ser Ile Phe Leu Val Thr Gly Gln Gln Val Asp Tyr Ser 355 360 365

Ile Ile Ala Ser Gln Ala Gly Ala Thr Leu Asn Asn Leu Met Ser His 370 375 380

Ala Gln Glu Leu Val Ala Lys Leu Arg Ser Leu Gln Phe Asp Gln Arg 385 390 395 400

Glu Phe Val Cys Leu Lys Phe Leu Val Leu Phe Ser Leu Asp Val Lys 405 410 415

Asn Leu Glu Asn Phe Gln Leu Val Glu Gly Val Gln Glu Gln Val Asn 420 425 430

Ala Ala Leu Leu Asp Tyr Thr Met Cys Asn Tyr Pro Gln Gln Thr Glu 435 440 445

Lys Phe Gly Gln Leu Leu Leu Arg Leu Pro Glu Ile Arg Ala Ile Ser 450 455 460

Met Gln Ala Glu Glu Tyr Leu Tyr Tyr Lys His Leu Asn Gly Asp Val 465 470 475 480

Pro Tyr Asn Asn Leu Leu Ile Glu Met Leu His Ala Lys Arg Ala 485 490 490

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<213> Human

<400> 157

Met Thr Ser Glu Glu Met Thr Ala Ser Val Leu Ile Pro Val Thr Gln

1 5 10 15

Arg Lys Val Val Ser Ala Gln Ser Ala Ala Asp Glu Ser Ser Glu Lys 20 25 30

Val Ser Asp Ile Asn Ile Ser Lys Ala His Thr Val Arg Arg Ser Gly 35 40 45

Glu Thr Ser His Thr Ile Ser Gln Leu Asn Lys Leu Lys Glu Glu Pro 50 60

Ser Gly Ser Asn Leu Pro Lys Ile Leu Ser Ile Ala Arg Glu Lys Ile 65 70 75 80

Val Ser Asp Glu Asn Ser Asn Glu Lys Cys Trp Glu Lys Ile Met Pro 85 90 95

Asp Ser Ala Lys Asn Leu Asn Ile Asn Cys Asn Asn Ile Leu Arg Asn 100 105 110 .

His Gln His Gly Leu Pro Gln Arg Gln Phe Tyr Glu Met Tyr Asn Ser 115 120 125

Val Ala Glu Glu Asp Leu Cys Leu Glu Thr Gly Ile Pro Ser Pro Leu 130 135 140

Glu Arg Lys Val Phe Pro Gly Ile Gln Leu Glu Leu Asp Arg Pro Ser 145 150 155 160

Met Gly Ile Ser Pro Leu Gly Asn Gln Ser Val Ile Ile Glu Thr Gly 165 170 175

Arg Ala His Pro Asp Ser Arg Arg Ala Val Phe His Phe His Tyr Glu 180 185 190

Val Asp Arg Arg Met Ser Asp Thr Phe Cys Thr Leu Ser Glu Asn Leu 195 200 205

Ile Leu Asp Asp Cys Gly Asn Cys Val Pro Leu Pro Gly Gly Glu Glu 210 215 220

Lys Gln Lys Lys Asn Tyr Val Ala Tyr Thr Cys Lys Leu Met Glu Leu 225 230 235 240

AIA	туѕ	Asn	Cys	Asp 245	Asn	ьуѕ	Asn	GLu	250	Leu	GIn	Cys	Asp	H1s 255	Cys
Asp	Thr	Leu	Asn 260	Asp	Lys	Tyr	Phe	Cys 265	Phe	Glu	Gly	Ser	Cys 270	Glu	Lys
Val	Asp	Met 275	Val	Tyr	Ser	Gly	Asp 280	Ser	Phe	Cys	Arg	Lys 285	Asp	Phe	Thr
Asp	Ser 290	Gln	Ala	Ala	Lys	Thr 295	Phe	Leu	Ser	His	Phe 300	Glu	Asp	Phe	Pro
Asp 305	Asn	Cys	Asp	Asp	Val 310	Glu	Glu	Asp	Ala	Phe 315	Lys	Ser	Lys	Lys	Glu 320
Arg	Ser	Thr	Leu	Leu 325	Val	Arg	Arg	Phe	Cys 330	Lys	Asn	Asp	Arg	Glu 335	Val
Lys	Lys	Ser	Val 340	Tyr	Thr	Gly	Thr	Arg 345	Ala	Ile	Val	Arg	Thr 350	Leu	Pro
Ser	Gly	His 355	Ile	Gly	Leu	Thr	Ala 360	Trp	Ser	Tyr	Ile	Asp 365	Gln	Lys	Arg
Asn	Gly 370	Pro	Leu	Leu	Pro	Cys 375	Gly	Arg	Val	Met	Glu 380	Pro	Pro	Ser	Thr
Val 385	Glu	Ile	Arg	Gln	Asp 390	Gly	Ser	Gln	Arg	Leu 395	Ser	Glu	Ala	Gln	Trp 400
Tyr	Pro	Ile	Tyr	Asn 405	Ala	Val	Arg	Arg	Glu 410	Glu	Thr	Glu	Asn	Thr 415	Val
Gly	Ser	Leu	Leu 420	His	Phe	Leu	Thr	Lys 425	Leu	Pro	Ala	Ser	Glu 430	Thr	Ala
His	Gly	Arg 435	Ile	Ser	Val	Gly	Pro 440	Cys	Leu	Lys	Gln	Cys 445	Val	Arg	Asp
Thr	Val 450	Cys	Glu	Tyr	Arg	Ala 455	Thr	Leu	Gln	Arg	Thr 460	Ser	Ile	Ser	Gln
Tyr 465	Ile	Thr	Gly	Ser	Leu 470	Leu	Glu	Ala	Thr	Thr 475	Ser	Leu	Gly	Ala	Arg 480

Ser Gly Leu Leu Ser Thr Phe Gly Gly Ser Thr Gly Arg Met Met Leu 485 490 Lys Glu Arg Gln Pro Gly Pro Ser Val Ala Asn Ser Asn Ala Leu Pro Ser Ser Ser Ala Gly Ile Ser Lys Glu Leu Ile Asp Leu Gln Pro Leu 520 Ile Gln Phe Pro Glu Glu Val Ala Ser Ile Leu Met Glu Gln Glu Gln 535 Thr Ile Tyr Arg Arg Val Leu Pro Val Asp Tyr Leu Cys Phe Leu Thr 550 555 Arg Asp Leu Gly Thr Pro Glu Cys Gln Ser Ser Leu Pro Cys Leu Lys 565 570 Ala Ser Ile Ser Ala Ser Ile Leu Thr Thr Gln Asn Gly Glu His Asn 585 580 590 Ala Leu Glu Asp Leu Val Met Arg Phe Asn Glu Val Ser Ser Trp Val 595 600 Thr Trp Leu Ile Leu Thr Ala Gly Ser Met Glu Glu Lys Arg Glu Val 610 Phe Ser Tyr Leu Val His Val Ala Lys Cys Cys Trp Asn Met Gly Asn 625 630 Tyr Asn Ala Val Met Glu Phe Leu Ala Gly Leu Arg Ser Arg Lys Val Leu Lys Met Trp Gln Phe Met Asp Gln Ser Asp Ile Glu Thr Met Arg 660 665 . 670 Ser Leu Lys Asp Ala Met Ala Gln His Glu Ser Ser Cys Glu Tyr Arg 675 Lys Val Val Thr Arg Ala Leu His Ile Pro Gly Cys Lys Val Val Pro 690 695 Phe Cys Gly Val Phe Leu Lys Glu Leu Cys Glu Val' Leu Asp Gly Ala 705 710 715 720

Ser Gly Leu Met Lys Leu Cys Pro Arg Tyr Asn Ser Gln Glu Glu Thr 725 730 735

Leu Glu Phe Val Ala Asp Tyr Ser Gly Gln Asp Asn Phe Leu Gln Arg 740 745 750

Val Gly Gln Asn Gly Leu Lys Asn Ser Glu Lys Glu Ser Thr Val Asn 755 760 765

Ser Ile Phe Gln Val Ile Arg Ser Cys Asn Arg Ser Leu Glu Thr Asp 770 775 780

Glu Glu Asp Ser Pro Ser Glu Gly Asn Ser Ser Arg Lys Ser Ser Leu 785 790 795 800

Lys Asp Lys Ser Arg Trp Gln Phe Ile Ile Gly Asp Leu Leu Asp Ser 805

Asp Asn Asp Ile Phe Glu Gln Ser Lys Glu Tyr Asp Ser His Gly Ser 820 825

Glu Asp Ser Gln Lys Ala Phe Asp His Gly Thr Glu Leu Ile Pro Trp 835 840 845

Tyr Val Leu Ser Ile Gln Ala Asp Val His Gln Phe Leu Leu Gln Gly 850 855

Ala Thr Val Ile His Tyr Asp Gln Asp Thr His Leu Ser Ala Arg Cys 865 870 875

Phe Leu Gln Leu Gln Pro Asp Asn Ser Thr Leu Thr Trp Val Lys Pro 885 890 895

Thr Thr Ala Ser Pro Ala Ser Ser Lys Ala Lys Leu Gly Val Leu Asn 900 905 910

Asn Thr Ala Glu Pro Gly Lys Phe Pro Leu Leu Gly Asn Ala Gly Leu 915 920 925

Ser Ser Leu Thr Glu Gly Val Leu Asp Leu Phe Ala Val Lys Ala Val 930 935

Tyr Met Gly His Pro Gly Ile Asp Ile His Thr Val Cys Val Gln Asn

945 950 955 960

Lys Leu Gly Ser Met Phe Leu Ser Glu Thr Gly Val Thr Leu Leu Tyr 965 970 975

- Gly Leu Gln Thr Thr Asp Asn Arg Leu Leu His Phe Val Ala Pro Lys 980 985 990
- His Thr Ala Lys Met Leu Phe Ser Gly Leu Leu Glu Leu Thr Arg Ala 995 1000 1005
- Val Arg Lys Met Arg Lys Phe Pro Asp Gln Arg Gln Gln Trp Leu 1010 1015 1020
- Arg Lys Gln Tyr Val Ser Leu Tyr Gln Glu Asp Gly Arg Tyr Glu 1025 1030 1035
- Gly Pro Thr Leu Ala His Ala Val Glu Leu Phe Gly Gly Arg Arg 1040 $$ 1045 $$ 1050
- Glu Lys Pro Asn Met Gln Arg Asn Asn Thr Leu Gly Ile Ser Thr 1070 \$1075\$
- Thr Lys Lys Lys Lys Ile Leu Met Arg Gly Glu Ser Gly Glu 1085
- Val Thr Asp Asp Glu Met Ala Thr Arg Lys Ala Lys Met His Lys 1100 1105 1110
- Glu Cys Arg Ser Arg Ser Gly Ser Asp Pro Gln Asp Ile Asn Glu 1115 1120 1125
- Gln Glu Glu Ser Glu Val Asn Ala Ile Ala Asn Pro Pro Asn Pro 1130 1135 1140
- Leu Pro Ser Arg Arg Ala His Ser Leu Thr Thr Ala Gly Ser Pro 1145 1150 1155
- Asn Leu Ala Ala Gly Thr Ser Ser Pro Ile Arg Pro Val Ser Ser 1160 1165 1170

Pro	Val 1175		Ser	Ser	Ser	Asn 1180	Lys	Ser	Pro	Ser	Ser 1185	Ala	Trp	Ser
Ser	Ser 1190	Ser	Trp	His	Gly	Arg 1195	Ile	Lys	Gly	Gly	Met 1200	Lys	Gly	Phe
Gln	Ser 1205		Met	Val	Ser	Asp 1210	Ser	Asn	Met	Ser	Phe 1215	Val	Glu	Phe
Val	Glu 1220		Phe	Lys	Ser	Phe 1225	Ser	Val	Arg	Ser	Arg 1230	Lys	Asp	Leu
Lys	Asp 1235		Phe	Asp	Val	Tyr 1240	Ala	Val	Pro	Суз	Asn 1245	Arg	Ser	Gly
Ser	Glu 1250		Ala	Pro	Leu	Tyr 1255	Thr	Asn	Leu	Thr	Ile 1260	Asp	Glu	Asn
Thr	Ser 1265		Leu	Gln	Pro	Asp 1270	Leu	Asp	Leu	Leu	Thr 1275	Arg	Asn	Val
Ser	Asp 1280		Gly	Leu	Phe	Ile 1285	Lys	Ser	Lys	Gln	Gln 1290	Leu	Ser	Asp
Asn	Gln 1295		, Gln	Ile	Ser	Asp 1300	Ala	Ile	Ala	Ala	Ala 1305	Ser	Ile	Val
Thr	Asn 1310		7 Thr	: Gly	Ile	Glu 1315	Ser	Thr	Ser	Leu	Gly 1320	Ile	Phe	Gly
Val	Gly 1325	Il∈ 5	e Leu	ı Gln	Leu	Asn 1330	Asp	Phe	Leu	Val	Asn 1335	Cys	Gln	Gly
Glu	1340		3 Thi	туг	: Asp	Glu 1345	Ile	Leu	ı Ser	·Ile	: Ile 1350	Glr	ı Lys	: Phe
Glı	1 Pro 135		r Ile	e Ser	Met	Cys 1360	His	Glr	ı Gly	, Leu	Met 1365	Sei	r Phe	e Glu
Gl	y Phe 137		a Ar	g Phe	e Let	1 Met 1375		ь Гуз	s Glu	ı Asr	n Phe 1380	Ala O	a Sei	Lys
Ası	n Asp 138		u Se:	r Glr	n Glu	ı Asn 1390		e Lys	s Glu	ı Leı	139	Le:	ı Pro	o Leu

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Ser	Tyr 1400	Tyr	Tyr	Ile	Glu	Ser 1405	Ser	His	Asn	Thr	Tyr 1410	Leu	Thr	Gly
His	Gln 1415	Leu	Lys	Gly	Glu	Ser 1420	Ser	Val	Glu	Leu	Tyr 1425	Ser	Gln	Val
Leu	Leu 1430		Gly	Cys	Arg	Ser 1435	Val	Glu	Leu	Asp	Cys 1440	Trp	Asp	Gly
Asp	Asp 1445		Met	Pro	Ile	Ile 1450	Tyr	His	Gly	His	Thr 1455	Pro	Thr	Thr
Lys	Ile 1460		Phe	Lys	Glu	Val 1465	Val	Glu	Ala	Ile	Asp 1470	Arg	Ser	Ala
Phe	Ile 1475		Ser	Asp	Leu	Pro 1480		Ile	Ile	Ser	Ile 1485	Glu	Asn	His
Cys	Ser 1490		Pro	Gln	Gln	Arg 1495		Met	Ala	Glu	Ile 1500	Phe	Lys	Thr
Val	Phe 1505		Glu	Lys	Leu	Val 1510		Lys	Phe	Leu	Phe 1515	Glu	Thr	Asp
Phe	Ser 1520		Asp	Pro	Met	Leu 1525		Ser	Pro	Asp	Gln 1530		Arg	Lys
Lys	Val 1535		Leu	Lys	Asn	Lys 1540		Leu	Lys	Ala	His 1545	Gln	Thr	Pro
Vål	Asp 1550	Ile	Leu	Lys	Gln	Lys 1555	Ala	His	Gln	Leu	Ala 1560	Ser	Met	Gln
Val	Gln 1565		Tyr	Asn	Gly	Gly 1570		Ala	Asn	Pro	Arg 1575	Pro	Ala	Asn
Asn	Glu 1580		Glu	Glu	. Asp	Glu 1585		Asp	Glu	ı Tyr	Asp 1590		Asp	Tyr
Glu	Ser 1595		ı Ser	: Asp	Asp	Asn 1600		: Leu	ı Glu	ı Asp	Arg 1605		Glu	Asn
Lys	Ser 1610		s Asn	a Asp) Lys	: Leu 1615		. Ph∈	e Glu	ı Tyr	Asn 1620	Glu	ı Glu	Ile

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Pro	Lys 1625		Ile	Lys	Lys	Ala 1630		Asn	Ser	Ala	Cys 1635		Lys	Gly
Lys	Val 1640	Tyr	Asp	Met	Glu	Leu 1645		Glu	Glu	Phe	Tyr 1650	Leu	Asp	Gln
Asn	Lys 1655		Glu	Ser	Arg	Gln 1660		Ala	Pro	Glu	Leu 1665	Ser	Asp	Leu
Val	Ile 1670	Tyr	Arg	Gln	Ala	Val 1675		Phe	Pro	Gly	Leu 1680	Ser	Thr	Leu
Asn	Ala 1685	Ser	Gly	Ser	Ser	Arg 1690		Lys	Glu	Arg	Lys 1695	Ser	Arg	Lys
Ser	Ile 1700	Phe	Gly	Asn	Asn	Pro 1705		Arg	Met	Ser	Pro 1710		Glu	Thr
Ala	Ser 1715	Phe	Asn	Lys	Thr	Ser 1720		Lys	Ser	Ser	Cys 1725	Glu	Gly	Ile
Arg	Gln 1730	Thr	Trp	Glu	Glu	Ser 1735		Ser	Pro	Leu	Asn 1740	Pro	Thr	Thr
Ser	Leu 1745	Ser	Ala	Ile	Ile	Arg 1750	Thr	Pro	Lys	Cys	Tyr 1755	His	Ile	Ser
Ser	Leu 1760	Asn	Glu	Asn	Ala	Ala 1765	Lys	Arg	Leu	Cys	Arg 1770	Arg	Tyr	Ser
Gln	Lys 1775										Leu 1785		Thr	Туг
Pro	Ala 1790	Ala	Thr	Arg	Ile	Asp 1795	Ser	Ser	Asn	Pro	Asn 1800	Pro	Leu	Met
Phe	Trp 1805	Leu	His	Gly	Ile	Gln 1810	Leu	Val	Ala	Leu	Asn 1815	Tyr	Gln	Thr
Asp	Asp 1820	Leu	Pro	Leu	His	Leu 1825	Asn	Ala	Ala	Met	Phe 1830	Glu	Ala	Asn
Gly	Gly	Cys	Gly	Туг	Val	Leu	Lys	Pro	Pro	Val	Leu	Trp	Asp	Lys

W/O 2004/0/2700	DCT/IIC2004/0002C0
WO 2004/063709	PCT/US2004/000368

	1835					1840					1845			
Asn	Cys 1850		Met	Tyr	Gln	Lys 1855			Pro		40.00		Asp	Leu
Asp	Ser 1865		Asp	Pro	Ala	Val 1870		Ser	Leu	Thr	Ile 1875		Ser	Gly
Gln	Asn 1880		Cys	Pro	Ser	Asn 1885		Met	Gly	Ser	Pro 1890	-	Ile	Glu
Val	Asp 1895		Leu	Gly	Met	Pro 1900	Leu	Asp	Ser	Cys	His 1905	Phe	Arg	Thr
Lys	Pro 1910		His	Arg	Asn	Thr 1915	Leu	Asn	Pro	Met	Trp 1920	Asn	Glu	Gln
Phe	Leu 1925	Phe	Arg	Val	His	Phe 1930	Glu	Äsp	Leu	Val	Phe 1935	Leu	Arg	Phe
Ala	Val 1940	Val	Glu	Asn	Asn	Ser 1945	Ser	Ala	Val	Thr	Ala 1950	Gln	Arg	Ile
Ile	Pro 1955	Leu	Lys	Ala	Leu	Lys 1960	Arg	Gly	Tyr	Arg	His 1965	Leu	Gln	Leu
Arg	Asn 1970	Leu	His	Asn	Glu	Val 1975	Leu	Glu	Ile	Ser	Ser 1980	Leu	Phe	Ile
Asn	Ser 1985	Arg	Arg	Met	Glu	Glu 1990	Asn	Ser	Ser	Gly	Asn 1995	Thr	Met	Ser
Ala	Ser 2000	Ser	Met	Phe	Asn	Thr 2005	Glu	Glu	Arg	Lys	Cys 2010	Leu	Gln	Thr
His	Arg 2015	Val	Thr	Val	His	Gly 2020	Val	Pro	Gly	Pro	Glu 2025	Pro	Phe	Thr
Val	Phe 2030	Thr	Ile	Asn	Gly	Gly 2035	Thr	Lys	Ala	Lys	Gln 2040	Leu	Leu	Gln
Gln	Ile 2045	Leu	Thr	Asn	Glu	Gln 2050	Asp	Ile	Lys	Pro	Val 2055	Thr	Thr	Asp

Tyr	Phe 2060	Leu	Met	Glu	Glu	Lys 2065	Tyr	Phe	Ile	Ser	Lys 2070	Glu	Lys	Asn
Glu	Cys 2075	Arg	Lys	Gln	Pro	Phe 2080	Gln	Arg	Ala	Ile	Gly 2085	Pro	Glu	Glu
Glu	Ile 2090	Met	Gln	Ile	Leu	Ser 2095	Ser	Trp	Phe	Pro	Glu 2100	Glu	Gly	Tyr
Met	Gly 2105	Arg	Ile	Val	Leu	Lys 2110		Gln	Gln	Glu	Asn 2115	Leu	Glu	Glu
Lys	Asn 2120		Val	Gln	Asp	Asp 2125	Lys	Glu	Val	Ile	Leu 2130	Ser	Ser	Glu
Glu	Glu 2135	Ser	Phe	Phe	Val	Gln 2140		His	Asp	Val	Ser 2145	Pro	Glu	Gln
Pro	Arg 2150		Val	Ile		Ala 2155	Pro	Arg	Val	Ser	Thr 2160	Ala	Gln	Asp
Val	Ile 2165	Gln	Gln	Thr		Cys 2170		Ala	Lys	Tyr_	Ser 2175	Tyr	Ser	Ile
Leu	Ser 2180	Asn	Pro	Asn	Pro	Ser 2185	Asp	Tyr	Val	Leu	Leu 2190	Glu	Glu	Val
Val	Lys 2195	Asp	Thr	Thr	Asn	Lys 2200		Thr	Thr	Thr	Pro 2205	Lys	Ser	Ser
						Gln 2215					Gln 2220		Gln	Ser
Lys	Trp 2225	Lys	Gly	Ala	Gly	Lys 2230	Phe	Ile	Leu	Lys	Leu 2235	Lys	Glu	Gln
Val	Gln 2240	Ala	Ser	Arg	Glu	Asp 2245	Lys	Lys	Lys	Gly	Ile 2250	Ser	Phe	Ala
Ser	Glu 2255	Leu	Lys	Lys	Leu	Thr 2260	Lys	Ser	Thr	Lys	Gln 2265	Pro	Arg	Gly
Leu	Thr 2270	Ser	Pro	Ser	Gln	Leu 2275	Leu	Thr	Ser	Glu	Ser 2280	Ile	Gln	Thr

Lys Glu Glu Lys Pro Val Gly Gly Leu Ser Pro Val Thr Gln Trp 2285

Ile Thr Asp Ser Asp 2300

<210> 158

<211> 303

<212> PRT

<213> Human

<400> 158

Met Ala Ser Trp Ala Lys Gly Arg Ser Tyr Leu Ala Pro Gly Leu Leu 1 5 10 15

Gln Gly Gln Val Ala Ile Val Thr Gly Gly Ala Thr Gly Ile Gly Lys 20 25 30

Ala Ile Val Lys Glu Leu Leu Glu Leu Gly Ser Asn Val Val Ile Ala 35 40 6 45

Ser Arg Lys Leu Glu Arg Leu Lys Ser Ala Ala Asp Glu Leu Gln Ala 50 55 60

Asn Leu Pro Pro Thr Lys Gln Ala Arg Val Ile Pro Ile Gln Cys Asn 65 70 75 80

Ile Arg Asn Glu Glu Glu Val Asn Asn Leu Val Lys Ser Thr Leu Asp 85 90 95

Leu Ser Pro Ala Glu His Ile Ser Ser Lys Gly Trp His Ala Val Leu 115 120 125

Glu Thr Asn Leu Thr Gly Thr Phe Tyr Met Cys Lys Ala Val Tyr Ser 130 140

Ser Trp Met Lys Glu His Gly Gly Ser Ile Val Asn Ile Ile Val Pro 145 150 155 160

Thr Lys Ala Gly Phe Pro Leu Ala Val His Ser Gly Ala Ala Arg Ala 165 170 175

Gly Val Tyr Asn Leu Thr Lys Ser Leu Ala Leu Glu Trp Ala Cys Ser

Gly Ile Arg Ile Asn Cys Val Ala Pro Gly Val Ile Tyr Ser Gln Thr 200

Ala Val Glu Asn Tyr Gly Ser Trp Gly Gln Ser Phe Phe Glu Gly Ser 215 210

Phe Gln Lys Ile Pro Ala Lys Arg Ile Gly Val Pro Glu Glu Val Ser 235 225 230

Ser Val Val Cys Phe Leu Leu Ser Pro Ala Ala Ser Phe Ile Thr Gly 250 245

Gln Ser Val Asp Val Asp Gly Gly Arg Ser Leu Tyr Thr His Ser Tyr 260 265

Glu Val Pro Asp His Asp Asn Trp Pro Lys Gly Ala Gly Asp Leu Ser 275 280

Val Val Lys Lys Met Lys Glu Thr Phe Lys Glu Lys Ala Lys Leu 295 300

<210> 159 <211> 246 <212> PRT

<213> Human

<400> 159

Met Glu Glu Ala Lys Ser Gln Ser Leu Glu Glu Asp Phe Glu Gly Gln

Ala Thr His Thr Gly Pro Lys Gly Val Ile Asn Asp Trp Arg Lys Phe 20

Lys Leu Glu Ser Gln Asp Ser Asp Ser Ile Pro Pro Ser Lys Lys Glu 40

Ile Leu Arg Gln Met Ser Ser Pro Gln Ser Arg Asn Gly Lys Asp Ser 55

Lys Glu Arg Val Ser Arg Lys Met Ser Ile Gln Glu Tyr Glu Leu Ile 75 65 70

His Lys Glu Lys Glu Asp Glu Asn Cys Leu Arg Lys Tyr Arg Arg Gln

Cys Met Gln Asp Met His Gln Lys Leu Ser Phe Gly Pro Arg Tyr Gly 105 110

Phe Val Tyr Glu Leu Glu Thr Gly Lys Gln Phe Leu Glu Thr Ile Glu 120

Lys Glu Leu Lys Ile Thr Thr Ile Val Val His Ile Tyr Glu Asp Gly 135

Ile Lys Gly Cys Asp Ala Leu Asn Ser Ser Leu Thr Cys Leu Ala Ala 155 150

Glu Tyr Pro Ile Val Lys Phe Cys Lys Ile Lys Ala Ser Asn Thr Gly 170

Ala Gly Asp Arg Phe Ser Leu Asp Val Leu Pro Thr Leu Leu Ile Tyr 185 180

Lys Gly Glu Leu Ile Ser Asn Phe Ile Ser Val Ala Glu Gln Phe 200 195

Ala Glu Glu Phe Phe Ala Gly Asp Val Glu Ser Phe Leu Asn Glu Tyr 210

Gly Leu Leu Pro Glu Arg Glu Val His Val Leu Glu His Thr Lys Ile 230 235 225

Glu Glu Glu Asp Val Glu 245

<210> 160 <211> 403 <212> PRT <213> Human

<400> 160

Met Thr Ala Ile Ile Lys Glu Ile Val Ser Arg Asn Lys Arg Arg Tyr

Gln Glu Asp Gly Phe Asp Leu Asp Leu Thr Tyr Ile Tyr Pro Asn Ile 25

Ile Ala Met Gly Phe Pro Ala Glu Arg Leu Glu Gly Val Tyr Arg Asn 40 Asn Ile Asp Asp Val Val Arg Phe Leu Asp Ser Lys His Lys Asn His Tyr Lys Ile Tyr Asn Leu Cys Ala Glu Arg His Tyr Asp Thr Ala Lys Phe Asn Cys Arg Val Ala Gln Tyr Pro Phe Glu Asp His Asn Pro Pro Gln Leu Glu Leu Ile Lys Pro Phe Cys Glu Asp Leu Asp Gln Trp Leu 105 Ser Glu Asp Asp Asn His Val Ala Ala Ile His Cys Lys Ala Gly Lys 115 120 Gly Arg Thr Gly Val Met Ile Cys Ala Tyr Leu Leu His Arg Gly Lys 130 135 Phe Leu Lys Ala Gln Glu Ala Leu Asp Phe Tyr Gly Glu Val Arg Thr 150 155 160 Arg Asp Lys Lys Gly Val Thr Ile Pro Ser Gln Arg Arg Tyr Val Tyr 165 170 175 Tyr Tyr Ser Tyr Leu Leu Lys Asn His Leu Asp Tyr Arg Pro Val Ala 185 190 180 Leu Leu Phe His Lys Met Met Phe Glu Thr Ile Pro Met Phe Ser Gly 195 200 Gly Thr Cys Asn Pro Gln Phe Val Val Cys Gln Leu Lys Val Lys Ile 210 Tyr Ser Ser Asn Ser Gly Pro Thr Arg Arg Glu Asp Lys Phe Met Tyr 230 235 240 Phe Glu Phe Pro Gln Pro Leu Pro Val Cys Gly Asp Ile Lys Val Glu 245 250 255 Phe Phe His Lys Gln Asn Lys Met Leu Lys Lys Asp Lys Met Phe His 260 265 270

Phe Trp Val Asn Thr Phe Phe Ile Pro Gly Pro Glu Glu Thr Ser Glu 275 280 285

Lys Val Glu Asn Gly Ser Leu Cys Asp Gln Glu Ile Asp Ser Ile Cys 290 295 300

Ser Ile Glu Arg Ala Asp Asn Asp Lys Glu Tyr Leu Val Leu Thr Leu 305 310 315 320

Thr Lys Asn Asp Leu Asp Lys Ala Asn Lys Asp Lys Ala Asn Arg Tyr 325 330 335

Phe Ser Pro Asn Phe Lys Val Lys Leu Tyr Phe Thr Lys Thr Val Glu 340 345 350

Glu Pro Ser Asn Pro Glu Ala Ser Ser Ser Thr Ser Val Thr Pro Asp 355 360 365

Val Ser Asp Asn Glu Pro Asp His Tyr Arg Tyr Ser Asp Thr Thr Asp 370 375 380

Ser Asp Pro Glu Asn Glu Pro Phe Asp Glu Asp Gln His Thr Gln Ile 385 390 395 400

Thr Lys Val

<210> 161

<211> 336

<212> PRT

<213> Human

<400> 161

Met Leu Gln Ser Leu Ala Gly Ser Ser Cys Val Arg Leu Val Glu Arg 1 5 10 15

His Arg Ser Ala Trp Cys Phe Gly Phe Leu Val Leu Gly Tyr Leu Leu 20 25 30

Tyr Leu Val Phe Gly Ala Val Val Phe Ser Ser Val Glu Leu Pro Tyr 35 40 45

Glu Asp Leu Leu Arg Gln Glu Leu Arg Lys Leu Lys Arg Arg Phe Leu 50 55 60

Glu Glu His Glu Cys Leu Ser Glu Gln Gln Leu Glu Gln Phe Leu Gly Arg Val Leu Glu Ala Ser Asn Tyr Gly Val Ser Val Leu Ser Asn Ala Ser Gly Asn Trp Asn Trp Asp Phe Thr Ser Ala Leu Phe Phe Ala Ser 100 105 110 Thr Val Leu Ser Thr Thr Gly Tyr Gly His Thr Val Pro Leu Ser Asp 115 120 Gly Gly Lys Ala Phe Cys Ile Ile Tyr Ser Val Ile Gly Ile Pro Phe 130 135 Thr Leu Leu Phe Leu Thr Ala Val Val Gln Arg Ile Thr Val His Val Thr Arg Arg Pro Val Leu Tyr Phe His Ile Arg Trp Gly Phe Ser Lys 170 Gln Val Val Ala Ile Val His Ala Val Leu Leu Gly Phe Val Thr Val 185 Ser Cys Phe Phe Ile Pro Ala Ala Val Phe Ser Val Leu Glu Asp 200 Asp Trp Asn Phe Leu Glu Ser Phe Tyr Phe Cys Phe Ile Ser Leu Ser 215 Thr Ile Gly Leu Gly Asp Tyr Val Pro Gly Glu Gly Tyr Asn Gln Lys

Phe Arg Glu Leu Tyr Lys Ile Gly Ile Thr Cys Tyr Leu Leu Leu Gly 245

230

Leu Ile Ala Met Leu Val Val Leu Glu Thr Phe Cys Glu Leu His Glu 260 265

Leu Lys Lys Phe Arg Lys Met Phe Tyr Val Lys Lys Asp Lys Asp Glu 275 280

Asp Gln Val His Ile Ile Glu His Asp Gln Leu Ser Phe Ser Ser Ile

235

250

290 295 300

Thr Asp Gln Ala Ala Gly Met Lys Glu Asp Gln Lys Gln Asn Glu Pro 305 310 315

Phe Val Ala Thr Gln Ser Ser Ala Cys Val Asp Gly Pro Ala Asn His 330

<210> 162

<211> 604 <212> PRT

<213> Human

<400> 162

Met Leu Ala Arg Ala Leu Leu Cys Ala Val Leu Ala Leu Ser His 10

Thr Ala Asn Pro Cys Cys Ser His Pro Cys Gln Asn Arg Gly Val Cys 25

Met Ser Val Gly Phe Asp Gln Tyr Lys Cys Asp Cys Thr Arg Thr Gly 40

Phe Tyr Gly Glu Asn Cys Ser Thr Pro Glu Phe Leu Thr Arg Ile Lys

Leu Phe Leu Lys Pro Thr Pro Asn Thr Val His Tyr Ile Leu Thr His 70

Phe Lys Gly Phe Trp Asn Val Val Asn Asn Ile Pro Phe Leu Arg Asn

Ala Ile Met Ser Tyr Val Leu Thr Ser Arg Ser His Leu Ile Asp Ser

Pro Pro Thr Tyr Asn Ala Asp Tyr Gly Tyr Lys Ser Trp Glu Ala Phe 125 .

Ser Asn Leu Ser Tyr Tyr Thr Arg Ala Leu Pro Pro Val Pro Asp Asp 135

Cys Pro Thr Pro Leu Gly Val Lys Gly Lys Lys Gln Leu Pro Asp Ser 150 155 160

Asn Glu Ile Val Glu Lys Leu Leu Arg Arg Lys Phe Ile Pro Asp

165 170 175

Pro Gln Gly Ser Asn Met Met Phe Ala Phe Phe Ala Gln His Phe Thr 180 185 190

His Gln Phe Phe Lys Thr Asp His Lys Arg Gly Pro Ala Phe Thr Asn 195 200 205

Gly Leu Gly His Gly Val Asp Leu Asn His Ile Tyr Gly Glu Thr Leu 210 215 220

Ala Arg Gln Arg Lys Leu Arg Leu Phe Lys Asp Gly Lys Met Lys Tyr 225 230 235 .240

Gln Ile Ile Asp Gly Glu Met Tyr Pro Pro Thr Val Lys Asp Thr Gln 245 250 255

Ala Glu Met Ile Tyr Pro Pro Gln Val Pro Glu His Leu Arg Phe Ala 260 265 270

Val Gly Gln Glu Val Phe Gly Leu Val Pro Gly Leu Met Met Tyr Ala 275 280 285

Thr Ile Trp Leu Arg Glu His Asn Arg Val Cys Asp Val Leu Lys Gln 290 295 300

Glu His Pro Glu Trp Gly Asp Glu Gln Leu Phe Gln Thr Ser Arg Leu 305 310 315 320

Ile Leu Ile Gly Glu Thr Ile Lys Ile Val Ile Glu Asp Tyr Val Gln
325 330 335

His Leu Ser Gly Tyr His Phe Lys Leu Lys Phe Asp Pro Glu Leu Leu 340 345 350

Phe Asn Lys Gln Phe Gln Tyr Gln Asn Arg Ile Ala Ala Glu Phe Asn 355 360 365

Thr Leu Tyr His Trp His Pro Leu Leu Pro Asp Thr Phe Gln Ile His 370 375 380

Asp Gln Lys Tyr Asn Tyr Gln Gln Phe Ile Tyr Asn Asn Ser Ile Leu 385 390 395

Leu Glu His Gly Ile Thr Gln Phe Val Glu Ser Phe Thr Arg Gln Ile 405 410 415

Ala Gly Arg Val Ala Gly Gly Arg Asn Val Pro Pro Ala Val Gln Lys 420 425 430

Val Ser Gln Ala Ser Ile Asp Gln Ser Arg Gln Met Lys Tyr Gln Ser 435 440 445

Phe Asn Glu Tyr Arg Lys Arg Phe Met Leu Lys Pro Tyr Glu Ser Phe 450 455 460

Glu Glu Leu Thr Gly Glu Lys Glu Met Ser Ala Glu Leu Glu Ala Leu 465 470 475 480

Tyr Gly Asp Ile Asp Ala Val Glu Leu Tyr Pro Ala Leu Leu Val Glu
485 490 495

Lys Pro Arg Pro Asp Ala Ile Phe Gly Glu Thr Met Val Glu Val Gly 500 505 510

Ala Pro Phe Ser Leu Lys Gly Leu Met Gly Asn Val Ile Cys Ser Pro 515 520 525

Ala Tyr Trp Lys Pro Ser Thr Phe Gly Gly Glu Val Gly Phe Gln Ile 530 540

Ile Asn Thr Ala Ser Ile Gln Ser Leu Ile Cys Asn Asn Val Lys Gly 545 550 555 560

Cys Pro Phe Thr Ser Phe Ser Val Pro Asp Pro Glu Leu Ile Lys Thr 565 570 575

Val Thr Ile Asn Ala Ser Ser Ser Arg Ser Gly Leu Asp Asp Ile Asn 580 585 590

Pro Thr Val Leu Leu Lys Glu Arg Ser Thr Glu Leu 595 600

<210> 163

<211> 117

<212> PRT

<213> Human

<400> 163

Met Arg Ala Ser Ser Phe Leu Ile Val Val Phe Leu Ile Ala Gly 1 5 10 15

Thr Leu Val Leu Glu Ala Ala Val Thr Gly Val Pro Val Lys Gly Gln 20 25 30

Asp Thr Val Lys Gly Arg Val Pro Phe Asn Gly Gln Asp Pro Val Lys 35 40 45

Gly Gln Val Ser Val Lys Gly Gln Asp Lys Val Lys Ala Gln Glu Pro 50 60

Val Lys Gly Pro Val Ser Thr Lys Pro Gly Ser Cys Pro Ile Ile Leu 65 70 75 80

Ile Arg Cys Ala Met Leu Asn Pro Pro Asn Arg Cys Leu Lys Asp Thr 85 90 95

Asp Cys Pro Gly Ile Lys Lys Cys Cys Glu Gly Ser Cys Gly Met Ala 100 105 110

Cys Phe Val Pro Gln 115

<210> 164

<211> 464

<212> PRT

<213> Human

<400> 164

Met Ala Gly Gln Asp Pro Ala Leu Ser Thr Ser His Pro Phe Tyr Asp

5 10 15

Val Ala Arg His Gly Ile Leu Gln Val Ala Gly Asp Asp Arg Phe Gly 20 25 30

Arg Arg Val Val Thr Phe Ser Cys Cys Arg Met Pro Pro Ser His Glu 35 40 45

Leu Asp His Gln Arg Leu Leu Glu Tyr Leu Lys Tyr Thr Leu Asp Gln 50 55 60

Tyr Val Glu Asn Asp Tyr Thr Ile Val Tyr Phe His Tyr Gly Leu Asn 65 70 75 80

Ser	Arg	Asn	Lys	Pro 85	Ser	Leu	Gly	Trp	Leu 90	Gln	Ser	Ala	Tyr	Lys 95	Glu
Phe	Asp	Arg	Lys 100	Asp	Gly	Asp	Leu	Thr 105	Met	Trp	Pro	Arg	Leu 110	Val	Ser
Asn	Ser	Lys 115	Leu	Lys	Arg	Ser	Ser 120	His	Leu	Ser	Leu	Pro 125	Lys	Tyr	Trp
Asp	Tyr 130	Arg	Tyr	Lys	Lys	Asn 135	Leu	Lys	Ala	Leu	Tyr 140	Val	Val	His	Pro
Thr 145	Ser	Phe	Ile	Lys	Val 150	Leu	Trp	Asn	Ile	Leu 155	Lys	Pro	Leu	Ile	Ser 160
His	Lys	Phe	Gly	Lys 165	Lys	Val	Ile	Tyr	Phe 170	Asn	Tyr	Leu	Ser	Glu 175	Leu
His	Glu	His	Leu 180	Lys	Tyr	Asp	Gln	Leu 185	Val	Ile	Pro	Pro	Glu 190	Val	Leu
Arg	Tyr	Asp 195	Glu	Lys	Leu	Gln	Ser 200	Leu	His	Glu	Gly	Arg 205	Thr	Pro	Pro
Pro	Thr 210	Lys	Thr	Pro	Pro	Pro 215	Arg	Pro	Pro	Leu	Pro 220	Thr	Gln	Gln	Phe
Gly 225	Val	Ser	Leu	Gln	Tyr 230	Leu	Lys	Asp	Lys	Asn 235	Gln	Gly	Glu	Leu	Ile 240
Pro	Pro	Val	Leu	Arg 245	Phe	Thr	Val	Thr	Tyr 250	Leu	Arg	Glu	Lys	Gly 255	Leu
Arg	Thr	Glu	Gly 260	Leu	Phe	Arg	Arg	Ser 265	Ala	Ser	Val	Gln	Thr 270	Val	Arg
Glu	Ile	Gln 275	Arg	Leu	Tyr	Asn	Gln 280	Gly	Lys	Pro	Val	Asn 285	Phe	Asp	Asp
Tyr	Gly 290	Asp	Ile	His	Ile	Pro 295	Ala	Val	Ile	Leu	Lys 300	Thr	Phe	Leu	Arg
Glu 305	Leu	Pro	Gln	Pro	Leu 310	Leu	Thr	Phe	Gln	Ala 315	Tyr	Glu	Gln	Ile	Leu 320

Gly Ile Thr Cys Val Glu Ser Ser Leu Arg Val Thr Gly Cys Arg Gln 325 330 335

Ile Leu Arg Ser Leu Pro Glu His Asn Tyr Val Val Leu Arg Tyr Leu 340 345 350

Met Gly Phe Leu His Ala Val Ser Arg Glu Ser Ile Phe Asn Lys Met 355 360 365

Asn Ser Ser Asn Leu Ala Cys Val Phe Gly Leu Asn Leu Ile Trp Pro 370 380

Ser Gln Gly Val Ser Ser Leu Ser Ala Leu Val Pro Leu Asn Met Phe 385 390 395 400

Thr Glu Leu Leu Ile Glu Tyr Tyr Glu Lys Ile Phe Ser Thr Pro Glu 405 410 415

Ala Pro Gly Glu His Gly Leu Ala Pro Trp Glu Gln Gly Ser Arg Ala 420 425 430

Ala Pro Leu Gln Glu Ala Val Pro Arg Thr Gln Ala Thr Gly Leu Thr 435 440 445

Lys Pro Thr Leu Pro Pro Ser Pro Leu Met Ala Ala Arg Arg Arg Leu 450 455 460

<210> 165

<211> 156

<212> PRT

<213> Human

<400> 165

Met Ala Leu Glu Lys Ser Leu Val Arg Leu Leu Leu Val Leu Ile 1 5 10 15

Leu Leu Val Leu Gly Trp Val Gln Pro Ser Leu Gly Lys Glu Ser Arg 20 25 30

Ala Lys Lys Phe Gln Arg Gln His Met Asp Ser Asp Ser Ser Pro Ser 35 40 45

Ser Ser Ser Thr Tyr Cys Asn Gln Met Met Arg Arg Arg Asn Met Thr 50 55 60

Gln Gly Arg Cys Lys Pro Val Asn Thr Phe Val His Glu Pro Leu Val 65 70 75 80

Asp Val Gln Asn Val Cys Phe Gln Glu Lys Val Thr Cys Lys Asn Gly 85 90 95

Gln Gly Asn Cys Tyr Lys Ser Asn Ser Ser Met His Ile Thr Asp Cys
100 105 110

Arg Leu Thr Asn Gly Ser Arg Tyr Pro Asn Cys Ala Tyr Arg Thr Ser 115 120 125

Pro Lys Glu Arg His Ile Ile Val Ala Cys Glu Gly Ser Pro Tyr Val 130 135 140

Pro Val His Phe Asp Ala Ser Val Glu Asp Ser Thr 145 150 155

<210> 166

<211> 375

<212> PRT

<213> Human

<400> 166

Met Asp Ala Leu Gln Leu Ala Asn Ser Ala Phe Ala Val Asp Leu Phe 1 5 10 15

Lys Gln Leu Cys Glu Lys Glu Pro Leu Gly Asn Val Leu Phe Ser Pro 20 25 30

Ile Cys Leu Ser Thr Ser Leu Ser Leu Ala Gl
n Val Gly Ala Lys Gly 35 40 45

Asp Thr Ala Asn Glu Ile Gly Gln Val Leu His Phe Glu Asn Val Lys 50 55 60

Asp Ile Pro Phe Gly Phe Gln Thr Val Thr Ser Asp Val Asn Lys Leu 65 70 75 80

Ser Ser Phe Tyr Ser Leu Lys Leu Ile Lys Arg Leu Tyr Val Asp Lys 85 90 95

Ser Leu Asn Leu Ser Thr Glu Phe Ile Ser Ser Thr Lys Arg Pro Tyr 100 105 110

- -

Ala Lys Glu Leu Glu Thr Val Asp Phe Lys Asp Lys Leu Glu Glu Thr 120 Lys Gly Gln Ile Asn Asn Ser Ile Lys Asp Leu Thr Asp Gly His Phe 135 Glu Asn Ile Leu Ala Asp Asn Ser Val Asn Asp Gln Thr Lys Ile Leu 150 Val Val Asn Ala Ala Tyr Phe Val Gly Lys Trp Met Lys Lys Phe Pro 170 165 Glu Ser Glu Thr Lys Glu Cys Pro Phe Arg Leu Asn Lys Thr Asp Thr 185 Lys Pro Val Gln Met Met Asn Met Glu Ala Thr Phe Cys Met Gly Asn 200 Ile Asp Ser Ile Asn Cys Lys Ile Ile Glu Leu Pro Phe Gln Asn Lys His Leu Ser Met Phe Ile Leu Leu Pro Lys Asp Val Glu Asp Glu Ser 230 235 Thr Gly Leu Glu Lys Ile Glu Lys Gln Leu Asn Ser Glu Ser Leu Ser 245 Gln Trp Thr Asn Pro Ser Thr Met Ala Asn Ala Lys Val Lys Leu Ser 265 260 Ile Pro Lys Phe Lys Val Glu Lys Met Ile Asp Pro Lys Ala Cys Leu 280 275 Glu Asn Leu Gly Leu Lys His Ile Phe Ser Glu Asp Thr Ser Asp Phe 295 290 Ser Gly Met Ser Glu Thr Lys Gly Val Ala Leu Ser Asn Val Ile His 305 310 Lys Val Cys Leu Glu Ile Thr Glu Asp Gly Gly Asp Ser Ile Glu Val 330 Pro Gly Ala Arg Ile Leu Gln His Lys Asp Glu Leu Asn Ala Asp His 340 345

Pro Phe Ile Tyr Ile Ile Arg His Asn Lys Thr Arg Asn Ile Ile Phe 360

Phe Gly Lys Phe Cys Ser Pro

<210> 167

<211> 240 <212> PRT

<213> Human

<400> 167

Met Leu Ala Leu Leu Cys Ser Cys Leu Leu Leu Ala Ala Gly Ala Ser

Asp Ala Trp Thr Gly Glu Asp Ser Ala Glu Pro Asn Ser Asp Ser Ala

Glu Trp Ile Arg Asp Met Tyr Ala Lys Val Thr Glu Ile Trp Gln Glu 40

Val Met Gln Arg Arg Asp Asp Asp Gly Thr Leu His Ala Ala Cys Gln

Val Gln Pro Ser Ala Thr Leu Asp Ala Ala Gln Pro Arg Val Thr Gly

Val Val Leu Phe Arg Gln Leu Ala Pro Arg Ala Lys Leu Asp Ala Phe 85 90

Phe Ala Leu Glu Gly Phe Pro Thr Glu Pro Asn Ser Ser Ser Arg Ala 100 105

Ile His Val His Gln Phe Gly Asp Leu Ser Gln Gly Cys Glu Ser Thr 115 120

Gly Pro His Tyr Asn Pro Leu Ala Val Pro His Pro Gln His Pro Gly 130 135

Asp Phe Gly Asn Phe Ala Val Arg Asp Gly Ser Leu Trp Arg Tyr Arg 145 150

Ala Gly Leu Ala Ala Ser Leu Ala Gly Pro His Ser Ile Val Gly Arg 165 170

Ala Val Val His Ala Gly Glu Asp Asp Leu Gly Arg Gly Gly Asn 180 185 190

Gln Ala Ser Val Glu Asn Gly Asn Ala Gly Arg Arg Leu Ala Cys Cys 195 200 205

Val Val Gly Val Cys Gly Pro Gly Leu Trp Glu Arg Gln Ala Arg Glu 210 215 220

His Ser Glu Arg Lys Lys Arg Arg Glu Ser Glu Cys Lys Ala Ala 225 230 235 240

<210> 168

<211> 283

<212> PRT

<213> Human

<400> 168

Met Glu Pro Pro Gly Asp Trp Gly Pro Pro Pro Trp Arg Ser Thr Pro 1 5 10 15

Arg Thr Asp Val Leu Arg Leu Val Leu Tyr Leu Thr Phe Leu Gly Ala 20 25 30

Pro Cys Tyr Ala Pro Ala Leu Pro Ser Cys Lys Glu Asp Glu Tyr Pro 35 40 45

Val Gly Ser Glu Cys Cys Pro Lys Cys Ser Pro Gly Tyr Arg Val Lys 50 55 60

Glu Ala Cys Gly Glu Leu Thr Gly Thr Val Cys Glu Pro Cys Pro Pro 65 70 75 80

Gly Thr Tyr Ile Ala His Leu Asn Gly Leu Ser Lys Cys Leu Gln Cys 85 90 95

Gln Met Cys Asp Pro Ala Met Gly Leu Arg Ala Ser Arg Asn Cys Ser 100 105 110

Arg Thr Glu Asn Ala Val Cys Gly Cys Ser Pro Gly His Phe Cys Ile 115 120 125

Val Gln Asp Gly Asp His Cys Ala Ala Cys Arg Ala Tyr Ala Thr Ser 130 135 140

Ser Pro Gly Gln Arg Val Gln Lys Gly Gly Thr Glu Ser Gln Asp Thr 145 150 155 160

Leu Cys Gln Asn Cys Pro Pro Gly Thr Phe Ser Pro Asn Gly Thr Leu 165 170 175

Glu Glu Cys Gln His Gln Thr Lys Cys Ser Trp Leu Val Thr Lys Ala 180 185 190

Gly Ala Gly Thr Ser Ser Ser His Trp Val Trp Trp Phe Leu Ser Gly 195 200 205

Ser Leu Val Ile Val Ile Val Cys Ser Thr Val Gly Leu Ile Ile Cys 210 215 220

Val Lys Arg Arg Lys Pro Arg Gly Asp Val Val Lys Val Ile Val Ser 225 230 235 240

Val Gln Arg Lys Arg Gln Glu Ala Glu Gly Glu Ala Thr Val Ile Glu 245 250 255

Ala Leu Gln Ala Pro Pro Asp Val Thr Thr Val Ala Val Glu Glu Thr 260 265 270

Ile Pro Ser Phe Thr Gly Arg Ser Pro Asn His 275 280

<210> 169

<211> 335

<212> PRT

<213> Human

<400> 169

Met Leu Gly Ile Trp Thr Leu Leu Pro Leu Val Leu Thr Ser Val Ala 1 5 10 15

Arg Leu Ser Ser Lys Ser Val Asn Ala Gln Val Thr Asp Ile Asn Ser 20 25 30

Lys Gly Leu Glu Leu Arg Lys Thr Val Thr Thr Val Glu Thr Gln Asn 35 40 45

Leu Glu Gly Leu His His Asp Gly Gln Phe Cys His Lys Pro Cys Pro 50 55 60

Pro 65	Gly	Glu	Arg	Lys	Ala 70	Arg	Asp	Cys	Thr	Val 75	Asn	Gly	Asp	Glu	Pro 80
Asp	Cys	Val	Pro	Cys 85	Gln	Glu	Gly	Lys	Glu 90	Tyr	Thr	Asp	Lys	Ala 95	His
Phe	Ser	Ser	Lys 100	Cys	Arg	Arg	Cys	Arg 105	Leu	Cys	Asp	Glu	Gly 110	His	Gly
Leu	Glu	Val 115	Glu	Ile	Asn	Cys	Thr 120	Arg	Thr	Gln	Asn	Thr 125	ГÀЗ	Суз	Arg
Cys	Lys 130	Pro	Asn	Phe	Phe	Cys 135	Asn	Ser	Thr	Val	Cys 140	Glu	His	Cys	Asp
Pro 145	Cys	Thr	Lys	Cys	Glu 150	His	Gly	Ile	Ile	Lys 155	Glu	Cys	Thr	Leu	Thr 160
Ser	Asn	Thr	Lys	Cys 165	Lys	Glu	Glu	Gly	Ser 170	Arg	Ser	Asn	Leu	Gly 175	Trp
Leu	Cys	Leu	Leu 180	Leu	Leu	Pro	Ile	Pro 185	Leu	Ile	Val	Trp	Val 190	Lys	Arg
Lys	Glu	Val 195	Gln	Lys	Thr	Cys	Arg 200	Lys	His	Arg	Lys	Glu 205	Asn	Gln	Gly
Ser	His 210	Glu	Ser	Pro	Thr	Leu 215	Asn	Pro	Glu	Thr	Val 220	Ala	Ile	Asn	Leu
Ser 225	Asp	Val	Asp	Leu	Ser 230	Lys	Tyr	Ile	Thr	Thr 235	Ile	Ala	Gly	Val	Met 240
Thr	Leu	Ser	Gln	Val 245	Lys	Gly	Phe	Val	Arg 250	Lys	Asn	Gly	Val	Asn 255	Glu
Ala	Lys	Ile	Asp 260	Glu	Ile	Lys	Asn	Asp 265	Asn	Val	Gln	Asp	Thr 270	Ala	Glu
Gln	Lys	Val 275	Gln	Leu	Leu	Arg	Asn 280	Trp	His	Gln	Leu	His 285	Gly	Lys	Lys
Glu	Ala	Туг	Asp	Thr	Leu	Ile	Lys	Asp	Leu	Lys	Lys	Ala	Asn	Leu	Cys

290 295 300

Thr Leu Ala Glu Lys Ile Gln Thr Ile Ile Leu Lys Asp Ile Thr Ser 305 310 315 320

Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val 325 330 335

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<400> 170

Met Asn Val Ala Arg Phe Leu Val Glu Lys His Thr Leu His Val Ile 1 5 10 15

Ile Asp Phe Ile Leu Ser Lys Val Ser Asn Gln Gln Ser Asn Leu Ala 20 25 30

Gln His Gln Arg Val Tyr Thr Gly Glu Lys Pro Tyr Lys Cys Asn Glu 35 40 45

Trp Gly Lys Ala Leu Ser Gly Lys Ser Ser Leu Phe Tyr His Gln Ala 50 55 60

Ile His Gly Val Gly Lys Leu Cys Lys Cys Asn Asp Cys His Lys Val 65 70 75 80

Phe Ser Asn Ala Thr Thr Ile Ala Asn His Trp Arg Ile His Asn Glu 85 90 95

Asp Arg Ser Tyr Lys Cys Asn Lys Cys Gly Lys Ile Phe Arg His Arg 100 105 110

Ser Tyr Leu Ala Val Tyr Gln Arg Thr His Thr Gly Glu Lys Pro Tyr 115 120 125

Lys Tyr His Asp Cys Gly Lys Val Phe Ser Gln Ala Ser Ser Tyr Ala 130 135 140

Lys His Arg Arg Ile His Thr Gly Glu Lys Pro His Lys Cys Asp Asp 145 150 155 160

Cys Gly Lys Val Leu Thr Ser Arg Ser His Leu Ile Arg His Gln Arg

165 170 175

Ile His Thr Gly Gln Lys Ser Tyr Lys Cys Leu Lys Cys Gly Lys Val 180 185 190

Phe Ser Leu Trp Ala Leu His Ala Glu His Gln Lys Ile His Phe 195 200 205

<210> 171

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<213> Human

<400> 171

Met Ala Ser Arg Ser Met Arg Leu Leu Leu Leu Leu Ser Cys Leu Ala 1 5 10 15

Lys Thr Gly Val Leu Gly Asp Ile Ile Met Arg Pro Ser Cys Ala Pro 20 25 30

Gly Trp Phe Tyr His Lys Ser Asn Cys Tyr Gly Tyr Phe Arg Lys Leu 35 40 45

Arg Asn Trp Ser Asp Ala Glu Leu Glu Cys Gln Ser Tyr Gly Asn Gly 50 60

Ala His Leu Ala Ser Ile Leu Ser Leu Lys Glu Ala Ser Thr Ile Ala 65 70 75 80

Glu Tyr Ile Ser Gly Tyr Gln Arg Ser Gln Pro Ile Trp Ile Gly Leu 85 90 95

His Asp Pro Gln Lys Arg Gln Gln Trp Gln Trp Ile Asp Gly Ala Met 100 105 110

Tyr Leu Tyr Arg Ser Trp Ser Gly Lys Ser Met Gly Gly Asn Lys His
115 120 125

Cys Ala Glu Met Ser Ser Asn Asn Asn Phe Leu Thr Trp Ser Ser Asn 130 135 140

Glu Cys Asn Lys Arg Gln His Phe Leu Cys Lys Tyr Arg Pro 145 150 155

<210> 172

<211> 432 <212> PRT <213> Human

<400> 172

Met Gly Pro Ala Gly Ser Leu Leu Gly Ser Gly Gln Met Gln Ile Thr 5 10 15

Leu Trp Gly Ser Leu Ala Ala Val Ala Ile Phe Phe Val Ile Thr Phe 20 25 30

Leu Ile Phe Pro Cys Ser Ser Cys Asp Arg Glu Lys Lys Pro Arg Gln 35 40 45

His Ser Gly Asp His Glu Asn Leu Met Asn Val Pro Ser Asp Lys Glu

Met Phe Ser Arg Ser Val Thr Ser Leu Ala Thr Asp Ala Pro Ala Ser 65 70 75

Ser Glu Gln Asn Gly Ala Leu Thr Asn Gly Asp Ile Leu Ser Glu Asp 90

Ser Thr Leu Thr Cys Met Gln His Tyr Glu Glu Val Gln Thr Ser Ala

Ser Asp Leu Leu Asp Ser Gln Asp Ser Thr Gly Lys Pro Lys Cys His 115 120

Gln Ser Arg Glu Leu Pro Arg Ile Pro Pro Glu Ser Ala Val Asp Thr 135

Met Leu Thr Ala Arg Ser Val Asp Gly Asp Gln Gly Leu Gly Met Glu 150 1.5.5

Gly Pro Tyr Glu Val Leu Lys Asp Ser Ser Ser Gln Glu Asn Met Val 165 170

Glu Asp Cys Leu Tyr Glu Thr Val Lys Glu Ile Lys Glu Val Ala Ala 185 180

Ala Ala His Leu Glu Lys Gly His Ser Gly Lys Ala Lys Ser Thr Ser 195 200 205

Ala Ser Lys Glu Leu Pro Gly Pro Gln Thr Glu Gly Lys Ala Glu Phe

215 220 210

Ala Glu Tyr Ala Ser Val Asp Arg Asn Lys Lys Cys Arg Gln Ser Val 235 230

Asn Val Glu Ser Ile Leu Gly Asn Ser Cys Asp Pro Glu Glu Glu Ala 250

Pro Pro Pro Val Pro Val Lys Leu Leu Asp Glu Asn Glu Asn Leu Gln 265

Glu Lys Glu Gly Gly Glu Ala Glu Glu Ser Ala Thr Asp Thr Thr Ser 280

Glu Thr Asn Lys Arq Phe Ser Ser Leu Ser Tyr Lys Ser Arq Glu Glu 295

Asp Pro Thr Leu Thr Glu Glu Glu Ile Ser Ala Met Tyr Ser Ser Val

Asn Lys Pro Gly Gln Leu Val Asn Lys Ser Gly Gln Ser Leu Thr Val 330

Pro Glu Ser Thr Tyr Thr Ser Ile Gln Gly Asp Pro Gln Arg Ser Pro

Ser Ser Cys Asn Asp Leu Tyr Ala Thr Val Lys Asp Phe Glu Lys Thr 355 360

Pro Asn Ser Thr Leu Pro Pro Ala Gly Arg Pro Ser Glu Glu Pro Glu 370 375

Pro Asp Tyr Glu Ala Ile Gln Thr Leu Asn Arg Glu Glu Glu Lys Ala 390 385 395

Thr Leu Gly Thr Asn Gly His His Gly Leu Val Pro Lys Glu Asn Asp 410 405

Tyr Glu Ser Ile Ser Asp Leu Gln Gln Gly Arg Asp Ile Thr Arg Leu 420 425

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<211> 174 <212> PRT

<213> Human

<400> 173

Lys Pro Phe Arg Cys Glu Asn Cys Asn Glu Arg Phe Gln Tyr Lys Tyr 1 5 10 15

Gln Leu Arg Ser His Met Ser Ile His Ile Gly His Lys Gln Phe Met 20 25 30

Cys Gln Trp Cys Gly Lys Asp Phe Asn Met Lys Gln Tyr Phe Asp Glu 35 40 45

His Met Lys Thr His Thr Gly Glu Lys Pro Tyr Ile Cys Glu Ile Cys 50 60

Gly Lys Ser Phe Thr Ser Arg Pro Asn Met Lys Arg His Arg Arg Thr 65 70 75 80

His Thr Gly Glu Lys Pro Tyr Pro Cys Asp Val Cys Gly Gln Arg Phe 85 90 95

Arg Phe Ser Asn Met Leu Lys Ala His Lys Glu Lys Cys Phe Arg Val 100 105 110

Ser His Thr Leu Ala Gly Asp Gly Val Pro Ala Ala Pro Gly Leu Pro 115 120 125

Pro Thr Gln Pro Gln Ala His Ala Leu Pro Leu Leu Pro Gly Leu Pro 130 135 140

Gln Thr Leu Pro Pro Pro Pro His Leu Pro Pro Pro Pro Pro Leu Phe 145 150 155 160

Pro Thr Thr Ala Ser Pro Gly Gly Arg Met Asn Ala Asn Asn 165 170

<210> 174

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<212> PRT

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Ala Ser Pro Arg Gly Thr Glu Ala Ser Pro Pro Gln Asn Asn Ser Gly 1 5 10 15

Ser Ser Ser Pro Val Phe Thr Phe Arg His Pro Leu Leu Ser Ser Gly

20 25 30

Gly Pro Gln Ser Pro Leu Arg Gly Ser Thr Gly Ser Leu Lys Ser Ser 35 40 45

Pro Ser Met Ser His Met Glu Ala Leu Gly Lys Ala Trp Asn Arg Gln 50 55 60

Leu Ser Arg Pro Leu Ser Gln Ala Val Ser Phe Ser Thr Pro Phe Gly 65 70 75 80

Leu Asp Ser Asp Val Asp Val Val Met Gly Asp Pro Val Leu Leu Arg 85 90 95

Ser Val Ser Ser Asp Ser Leu Gly Pro Pro Arg Pro Ala Pro Ala Arg 100 105 110

Thr Pro Thr Gln Pro Pro Pro Glu Pro Gly Asp Leu Pro Thr Ile Glu 115 120 125

Glu Ala Leu Gln Ile Ile His Ser Ala Glu Pro Arg Leu Leu Pro Asp 130 135 140

Gly Ala Ala Asp Gly Ser Phe Tyr Leu His Ser Pro Glu Gly Pro Ser 145 150 155 160

Lys Pro Ser Leu Ala Ser Pro Tyr Leu Pro Glu Gly Thr Ser Lys Pro \cdot 165 \cdot 170 \cdot 175

Leu Ser Asp Arg Pro Thr Lys Ala Pro Val Tyr Met Pro His Pro Glu 180 185 190

Thr Pro Ser Lys Pro Ser Pro Cys Leu Val Gly Glu Ala Ser Lys Pro $195 \hspace{1cm} 200 \hspace{1cm} 205 \hspace{1cm}$

Pro Ala Pro Ser Glu Gly Ser Pro Lys Ala Val Ala Ser Ser Pro Ala 210 215 220

Ala Thr Asn Ser Glu Val Lys Met Thr Ser Phe Ala Glu Arg Lys Lys 225 230 235 240

Gln Leu Val Lys Ala Glu Ala Glu Ala Gly Ala Gly Ser Pro Thr Ser $245 \hspace{1.5cm} 250 \hspace{1.5cm} 255$

Thr Pro Ala Pro Pro Glu Ala Leu Ser Ser Glu Met Ser Glu Leu Ser 260 265 Ala Arg Leu Glu Glu Lys Arg Arg Ala Ile Glu Ala Gln Lys Arg Arg 275 280 Ile Glu Ala Ile Phe Ala Lys His Arg Gln Arg Leu Gly Lys Ser Ala 290 295 Phe Leu Gln Val Gln Pro Arg Glu Ala Ser Gly Glu Ala Glu Ala Glu 310 315 320 Ala Glu Glu Ala Asp Ser Gly Pro Val Pro Gly Gly Glu Arg Pro Ala 325 330 Gly Glu Gly Gln Gly Glu Pro Thr Ser Arg Pro Lys Ala Val Thr Phe 345 Ser Pro Asp Leu Gly Pro Val Pro His Glu Gly Leu Gly Glu Tyr Asn 360 Arg Ala Val Ser Lys Leu Ser Ala Ala Leu Ser Ser Leu Gln Arg Asp Met Gln Arg Leu Thr Asp Gln Gln Gln Arg Leu Leu Ala Pro Pro Glu 390 Ala Pro Gly Ser Ala Pro Pro Pro Ala Ala Trp Val Ile Pro Gly Pro 410 Thr Thr Gly Pro Lys Ala Ala Ser Pro Ser Pro Ala Arg Arg Val Pro 420 425 Ala Thr Arg Arg Ser Pro Gly Pro Gly Pro Ser Gln Ser Pro Arg Ser 435 440 Pro Lys His Thr Arg Pro Ala Glu Leu Arg Leu Ala Pro Leu Thr Arg 455 460 450 Val Leu Thr Pro Pro His Asp Val Asp Ser Leu Pro His Leu Arg Lys 470 475 Phe Ser Pro Ser Gln Val Pro Val Gln Thr Arg Ser Ser Ile Leu Leu 485 490

Ala Glu Glu Thr Pro Pro Glu Glu Pro Ala Ala Arg Pro Gly Leu Ile 505 Glu Ile Pro Leu Gly Ser Leu Ala Asp Pro Ala Ala Glu Asp Glu Gly 515 520 525 Asp Gly Ser Pro Ala Gly Ala Glu Asp Ser Leu Glu Glu Glu Ala Ser 535 Ser Glu Gly Glu Pro Arg Val Gly Leu Gly Phe Phe Tyr Lys Asp Glu 550 555 Asp Lys Pro Glu Asp Glu Met Ala Gln Lys Arg Ala Ser Leu Leu Glu 570 Arg Gln Gln Arg Arg Ala Glu Glu Ala Arg Arg Arg Lys Gln Trp Gln Glu Val Glu Lys Glu Gln Arg Arg Glu Glu Ala Ala Arg Leu Ala Gln 600 Glu Glu Ala Pro Gly Pro Ala Pro Leu Val Ser Ala Val Pro Met Ala 615 Thr Pro Ala Pro Ala Ala Arg Ala Pro Ala Glu Glu Val Gly Pro 630 635 Arg Lys Gly Asp Phe Thr Arg Gln Glu Tyr Glu Arg Arg Ala Gln Leu 645 650 Lys Leu Met Asp Asp Leu Asp Lys Val Leu Arg Pro Arg Ala Ala Gly 665 Ser Gly Gly Pro Gly Arg Gly Gly Arg Arg Ala Thr Arg Pro Arg Ser 680 Gly Cys Cys Asp Asp Ser Ala Leu Ala Arg Ser Pro Ala Arg Gly Leu Leu Gly Ser Arg Leu Ser Lys Ile Tyr Ser Gln Ser Thr Leu Ser Leu 710 Ser Thr Val Ala Asn Glu Ala His Asn Asn Leu Gly Val Lys Arg Pro 730 725

Thr Ser Arg Ala Pro Ser Pro Ser Gly Leu Met Ser Pro Ser Arg Leu 745 740

Pro Gly Ser Arg Glu Arg Asp Trp Glu Asn Gly Ser Asn Ala Ser Ser 755 760 765

Pro Ala Ser Val Pro Glu Tyr Thr Gly Pro Arg Leu Tyr Lys Glu Pro 770 775

Ser Ala Lys Ser Asn Lys Phe Ile Ile His Asn Ala Leu Ser His Cys 785 790

Cys Leu Ala Gly Lys Val Asn Glu Pro Gln Lys Asn Arg Ile Leu Glu 805 810

Glu Ile Glu Lys Ser Lys Ala Asn His Phe Leu Ile Leu Phe Arg Asp 820 825

Ser Ser Cys Gln Phe Arg Ala Leu Tyr Thr Leu Ser Gly Glu Thr Glu 835 840 845

Glu Leu Ser Arg Leu Ala Gly Tyr Gly Pro Arg Thr Val Thr Pro Ala 850 855

Met Val Glu Gly Ile Tyr Lys Tyr Asn Ser Asp Arg Lys Arg Phe Thr 870 875

Gln Ile Pro Ala Lys Thr Met Ser Met Ser Val Asp Ala Phe Thr Ile 890 885

Gln Gly His Leu Trp Gln Gly Lys Lys Pro Thr Thr Pro Lys Lys Gly 910 900 905

Gly Gly Thr Pro Lys 915

<210> 175 <211> 600 <212> PRT <213> Human

<400> 175

Met Arg Ser Cys Leu Trp Arg Cys Arg His Leu Ser Gln Gly Val Gln 1 5

Trp Ser Leu Leu Leu Ala Val Leu Val Phe Phe Leu Phe Ala Leu Pro 20 Ser Phe Ile Lys Glu Pro Gln Thr Lys Pro Ser Arg His Gln Arg Thr Glu Asn Ile Lys Glu Arg Ser Leu Gln Ser Leu Ala Lys Pro Lys Ser Gln Ala Pro Thr Arg Ala Arg Arg Thr Thr Ile Tyr Ala Glu Pro Val 75 70 Pro Glu Asn Asn Ala Leu Asn Thr Gln Thr Gln Pro Lys Ala His Thr Thr Gly Asp Arg Gly Lys Glu Ala Asn Gln Ala Pro Pro Glu Glu Gln 100 Asp Lys Val Pro His Thr Ala Gln Arg Ala Ala Trp Lys Ser Pro Glu 120 Lys Glu Lys Thr Met Val Asn Thr Leu Ser Pro Arg Gly Gln Asp Ala 135 Gly Met Ala Ser Gly Arg Thr Glu Ala Gln Ser Trp Lys Ser Gln Asp 155 150 Thr Lys Thr Thr Gln Gly Asn Gly Gly Gln Thr Arg Lys Leu Thr Ala 170 165 Ser Arg Thr Val Ser Glu Lys His Gln Gly Lys Ala Ala Thr Thr Ala 180 185 Lys Thr Leu Ile Pro Lys Ser Gln His Arg Met Leu Ala Pro Thr Gly 200 Ala Val Ser Thr Arg Thr Arg Gln Lys Gly Val Thr Thr Ala Val Ile Pro Pro Lys Glu Lys Lys Pro Gln Ala Thr Pro Pro Pro Ala Pro Phe 235 Gln Ser Pro Thr Thr Gln Arg Asn Gln Arg Leu Lys Ala Ala Asn Phe

250 255 245 Lys Ser Glu Pro Arg Trp Asp Phe Glu Glu Lys Tyr Ser Phe Glu Ile 265 Gly Gly Leu Gln Thr Thr Cys Pro Asp Ser Val Lys Ile Lys Ala Ser 280 Lys Ser Leu Trp Leu Gln Lys Leu Phe Leu Pro Asn Leu Thr Leu Phe 295 Leu Asp Ser Arg His Phe Asn Gln Ser Glu Trp Asp Arg Leu Glu His Phe Ala Pro Pro Phe Gly Phe Met Glu Leu Asn Tyr Ser Leu Val Gln Lys Val Val Thr Arg Phe Pro Pro Val Pro Gln Gln Leu Leu Leu 345 Ala Ser Leu Pro Ala Gly Ser Leu Arg Cys Ile Thr Cys Ala Val Val 355 360 Gly Asn Gly Gly Ile Leu Asn Asn Ser His Met Gly Gln Glu Ile Asp 370 375 Ser His Asp Tyr Val Phe Arg Leu Ser Gly Ala Leu Ile Lys Gly Tyr 390 385 395

Glu Gln Asp Val Gly Thr Arg Thr Ser Phe Tyr Gly Phe Thr Ala Phe 405 410 415

Ser Leu Thr Gln Ser Leu Leu Ile Leu Gly Asn Arg Gly Phe Lys Asn 420 425 430

Val Pro Leu Gly Lys Asp Val Arg Tyr Leu His Phe Leu Glu Gly Thr 435 440 445

Arg Asp Tyr Glu Trp Leu Glu Ala Leu Leu Met Asn Gln Thr Val Met 450 455 460

Ser Lys Asn Leu Phe Trp Phe Arg His Arg Pro Gln Glu Ala Phe Arg 465 470 475 480

Glu Ala Leu His Met Asp Arg Tyr Leu Leu Leu His Pro Asp Phe Leu 485 490 495

Arg Tyr Met Lys Asn Arg Phe Leu Arg Ser Lys Thr Leu Asp Gly Ala 500 505 510

His Trp Arg Ile Tyr Arg Pro Thr Thr Gly Ala Leu Leu Leu Thr 515 520 525

Ala Leu Gln Leu Cys Asp Gln Val Ser Ala Tyr Gly Phe Ile Thr Glu 530 535 540

Gly His Glu Arg Phe Ser Asp His Tyr Tyr Asp Thr Ser Trp Lys Arg 545 550 555 560

Leu Ile Phe Tyr Ile Asn His Asp Phe Lys Leu Glu Arg Glu Val Trp 565 570 575

Lys Arg Leu His Asp Glu Gly Ile Ile Arg Leu Tyr Gln Arg Pro Gly 580 585 590

Pro Gly Thr Ala Lys Ala Lys Asn 595 600

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<211> 312

<212> PRT

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<400> 176

Met Asp Gly Glu Asn His Ser Val Val Ser Glu Phe Leu Phe Leu Gly 5 10 15

Leu Thr His Ser Trp Glu Ile Gln Leu Leu Leu Leu Val Phe Ser Ser 20 25 30

Val Leu Tyr Val Ala Ser Ile Thr Gly Asn Ile Leu Ile Val Phe Ser 35 40 45

Val Thr Thr Asp Pro His Leu His Ser Pro Met Tyr Phe Leu Leu Ala 50 55 60

Ser Leu Ser Phe Ile Asp Leu Gly Ala Cys Ser Val Thr Ser Pro Lys 70 75 80

Met Ile Tyr Asp Leu Phe Arg Lys Arg Lys Val Ile Ser Phe Gly Gly 85 90 Cys Ile Ala Gln Ile Phe Phe Ile His Val Ile Gly Gly Val Glu Met Val Leu Leu Ile Ala Met Ala Phe Asp Arg Tyr Val Ala Leu Cys Lys 120 Pro Leu His Tyr Leu Thr Ile Met Ser Pro Arg Met Cys Leu Ser Phe Leu Ala Val Ala Trp Thr Leu Gly Val Ser His Ser Leu Phe Gln Leu 150 Ala Phe Leu Val Asn Leu Ala Phe Cys Gly Pro Asn Val Leu Asp Ser 170 165 Phe Tyr Cys Asp Leu Pro Arg Leu Leu Arg Leu Ala Cys Thr Asp Thr 180 Tyr Arg Leu Gln Phe Met Val Thr Val Asn Ser Gly Phe Ile Cys Val 195 200 Gly Thr Phe Phe Ile Leu Leu Ile Ser Tyr Val Phe Ile Leu Phe Thr 215 Val Trp Lys His Ser Ser Gly Gly Ser Ser Lys Ala Leu Ser Thr Leu 235 230 Ser Ala His Ser Thr Val Val Leu Leu Phe Phe Gly Pro Pro Met Phe 245 250 Val Tyr Thr Arg Pro His Pro Asn Ser Gln Met Asp Lys Phe Leu Ala 265 Ile Phe Asp Ala Val Leu Thr Pro Phe Leu Asn Pro Val Val Tyr Thr Phe Arg Asn Lys Glu Met Lys Ala Ala Ile Lys Arg Val Cys Lys Gln 290 295 300 Leu Val Ile Tyr Lys Arg Ile Ser 310 305

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<211> 114

<212> PRT

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<400> 177

Met Ala Leu Glu His Leu Val Val Trp His Val His Ser Glu Asp Gln 10

Ser Phe Val Val Leu Lys Thr Asp Leu Gly Arg Arg Gly Cys Arg Pro

Leu Arg Lys Thr Ala Pro Lys Ala Lys Glu Ala Pro Ala Pro Pro Lys

Ala Glu Ala Lys Val Lys Ala Leu Lys Ala Lys Lys Ala Val Leu Lys

Gly Val Arg Ser His Thr Gln Lys Arg Arg Ser Ala Cys His Ser Pro

Ser Gly Gly Pro Arg His Cys Asp Ser Gly Gly Ser Pro Asp Ile Leu 90

Gly Arg Ala Pro Pro Gly Glu Thr Ser Leu Ala Thr Met Leu Ser Ser 105 100

Phe Arg

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<400> 178

Asp Ser Met Thr Phe Glu Asp Ile Ile Val Asp Phe Thr Gln Glu Glu 1

Trp Ala Leu Leu Asp Thr Ser Gln Arg Lys Leu Phe Gln Asp Val Met 25 20

Leu Glu Asn Ile Ser His Leu Val Ser Ile Gly Glu Asp Phe Thr Gln 35

His Ile Ala Leu Thr Gln Asn Val Ile Thr Tyr Met Arg Thr Lys His 50 Phe Val Ser Lys Lys Phe Gly Lys Ile Phe Ser Asp Trp Leu Ser Phe Asn Gln His Lys Glu Ile His Thr Lys Cys Lys Ser Tyr Gly Ser His 90 Leu Phe Asp Tyr Ala Phe Ile Gln Asn Ser Ala Leu Arg Pro His Ser Val Thr His Thr Arg Glu Ile Thr Leu Glu Cys Arg Val Cys Gly Lys Thr Phe Ser Lys Asn Ser Asn Leu Arg Arg His Glu Met Ile His Thr 135 Gly Glu Lys Pro His Gly Cys His Leu Cys Gly Lys Ala Phe Thr His 150 Cys Ser Asp Leu Arg Lys His Glu Arg Thr His Thr Gly Glu Lys Pro 165 170 Tyr Gly Cys His Leu Cys Gly Lys Ala Phe Ser Lys Ser Ser Asn Leu 180 1.85 Arg Arg His Glu Met Ile His Thr Arg Glu Lys Ala Gln Ile Cys His 200 195

Leu Cys Gly Lys Ala Phe Thr His Cys Ser Asp Leu Arg Lys His Glu 210 215 220

Arg Thr His Leu Gly Asp Lys Pro Tyr Gly Cys Leu Leu Cys Gly Lys 225 230 235 240

Ala Phe Ser Lys Cys Ser Tyr Leu Arg Gln His Glu Arg Thr His Asn 245 250 255

Gly Glu Lys Pro Tyr Glu Cys His Leu Cys Gly Lys Ala Phe Ser His 260 265 270

Cys Ser His Leu Arg Gln His Glu Arg Ser His Asn Gly Glu Lys Pro 275 280 285

His Gly Cys His Leu Cys Gly Lys Ala Phe Thr Glu Ser Ser Val Leu 295

Lys Arg His Glu Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys His 315

Val Cys Gly Lys Ala Phe Thr Glu Ser Ser Asp Leu Arg Arg His Glu 325

Arg Thr His Thr Gly Glu Lys Pro Tyr Glu Cys His Leu Cys Gly Lys 340

Ala Phe Asn His Ser Ser Val Leu Arg Arg His Glu Arg Thr His Thr 355 360

Gly Glu Lys Pro Tyr Glu Cys Asn Ile Cys Gly Lys Ala Phe Asn Arg 375 370

Ser Tyr Asn Phe Arg Leu His Arg Arg Val His Thr Gly Glu Lys Pro 395 390 385

Tyr Val Cys Pro Leu Cys Gly Lys Ala Phe Ser Lys Phe Phe Asn Leu 405 410

Arg Gln His Glu Arg Thr His Thr Lys Lys Ala Met Asn Met 425

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<210> 180

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Asn Tyr Gly Val His

<210> 181

<211> 48

436/439

15

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                             10
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gccctcacct actatgatta cgagtttgct tac
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Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr
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agggccagtc agagtattgg cacaaacata cac
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Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile His
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<210> <211> <212> <213>	PRT	
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Gln Gl 1	n Asn Asn Asn Trp Pro Thr Thr 5	
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<210><211><211><212><213>	19 DNA	
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gtgaccaggc gcccaatac		19	
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gcgtctcttg ccggaatgt			
5 5			
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	Artificial		
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